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SCLEROSIS OF THE HEPATIC VEINS IN CHRONIC CONGESTIVE HEART FAILURE

HARRY GROSS, M.D.

NEW YORK

It has been shown that a frequent site of arteriosclerotic change in a vessel is at a point of increased local intra-arterial tension. This relationship of chronically heightened intravascular pressure to the development of arteriosclerosis holds both for the lesser and for the greater circulation.

In the veins in which similar dynamic factors exist, sclerotic changes have been less frequently described. However, the veins have received relatively little study at the hands of pathologists, and the etiology of phlebosclerosis has been contested. While increased intra-arterial pressure is generally accepted as an important factor in the causation of arteriosclerosis, increased intravenous pressure alone is not universally conceded to be the cause of phlebosclerosis. Sclerosis of the veins has also been held to be associated with aging and to occur sometimes as part of a generalized vascular process. The latter view has, however, been questioned.

The purpose of this study was to determine whether long-standing increased pressure in the hepatic veins due to chronic congestive heart failure is regularly associated with sclerosis of these veins. These veins were studied in chronic heart failure of various types, namely, rheumatic, hypertensive and emphysema heart disease. In every case, failure of the right side of the heart and hepatic enlargement were present, making it necessary to assume the coexistence of hypertension in the lesser circulation and simultaneously increased tension within the hepatic veins.

REVIEW OF THE LITERATURE

Moschcowitz [1] contended that increased intravascular pressure is the sole cause of arteriosclerosis. Likewise he [2] held that phlebosclerosis

From the Medical Service of Dr. Leopold Lichtwitz, Montefiore Hospital.

1. Moschcowitz, E.: Am. Heart J. **6**:171, 1930.

2. Moschcowitz, E.: Phlebosclerosis of the Hepatic Veins, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 2, p. 857.

also is found only under conditions associated with increased intravenous pressure. Ljungdahl,[3] in a study of the lesser circulation, reported the frequent occurrence of pulmonary arteriosclerosis with the hypertension of the pulmonary circulation associated with mitral stenosis. However, in many of the cases the pulmonary veins as well as the arteries showed sclerosis. He observed greater sclerosis in the arteries than in the veins, the smallest veins never showing more than fibrous streaking. He attributed the greater changes in the arteries to higher pressure within these vessels and to nutritional disturbances. These factors would also explain the less frequent occurrence of phlebosclerosis as compared with arteriosclerosis. He pointed out the similarity of phlebosclerosis to arteriosclerosis and indicated the relationship between increased tension within the lumen and the degree of dilatation of a vessel. He noted that if the increased pressure was sufficiently great, the increased inflow resulted in the formation of an increase of connective tissue within the wall. Miller[4] also reported pulmonary arteriosclerosis and dilatation from the hypertension of the lesser circulation associated with mitral stenosis. Kaya[5] observed the frequent association of phlebosclerosis and chronic stasis. However, he doubted that congestive heart failure alone causes phlebosclerosis in young persons.

Further evidence that increased intravenous pressure plays a rôle in the etiology of phlebosclerosis is afforded by the work of Schilling,[6] who observed venous changes similar to arteriosclerosis in those sites which were under increased pressure. In a series of 75 cases, he noted that phlebosclerosis was due to congestion in 33 instances, and spoke of the part played by congestion in the production of the phlebosclerosis. Unlike Sack,[7] who was of the belief that phlebosclerosis is a part of a generalized vascular disease, Schilling[6] and Simmonds[8] upheld the independence of venous from arterial sclerosis. Hauswirth and Eisenberg[9] regarded phlebosclerosis as a disseminated process, which they found frequently in association with peptic ulcers. Changes in the inferior vena cava secondary to chronic congestive heart failure were recently denied by Allen and Page.[10]

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3. Ljungdahl, M.: Untersuchungen über die Arteriosklerose des kleinen Kreislaufs, Wiesbaden, J. F. Bergmann, 1915.

4. Miller, H. R.: M. Clin. North America **9**:673, 1925.

5. Kaya, R.: Virchows Arch. f. path. Anat. **189**:466, 1907.

6. Schilling, W.: Virchows Arch. f. path. Anat. **262**:658, 1926.

7. Sack, E.: Virchows Arch. f. path. Anat. **112**:403, 1888.

8. Simmonds, M.: Virchows Arch. f. path. Anat. **207**:360, 1912.

9. Hauswirth, L., and Eisenberg, A. A.: Arch. Path. **11**:858, 1931.

10. Allen, E. V., and Page, I. H.: Deutsches Arch. f. klin. Med. **168**:193, 1930.

Simmonds recorded sclerosis of the portal vein in portal cirrhosis, in which the increased venous tension made the dynamic factors similar to those of the chronically distended veins of the liver in congestive heart failure. Lossen [11] reported sclerosis of the portal, splenic, mesenteric and coronary veins in Banti's syndrome. He quoted Banti, who observed sclerosis of the splenic veins in the first stage of the disease and sclerosis in other branches of the portal system in the ascitic stage. Banti ascribed these changes to increased pressure from cirrhosis of the liver. McIndoe [12] recorded not only sclerosis of the portal system but also sclerosis of the hepatic veins in portal cirrhosis.

Following surgical arteriovenous anastomoses, long after operation, Carrel [13] noted scars at the points of anastomosis, especially if the vessels differed in caliber. The segment of vein reacted to the arterial pressure by an increase in the thickness and strength of its wall. There were proximal dilatation of the artery and enlargement and thickening of the vein, observed histologically to be due to hypertrophy. Reid [14] stated that in arteriovenous aneurysm the altered pressure was responsible for the final atrophy of the artery and hypertrophy of the vein. It is noteworthy that in a woman of 34 with an arteriovenous fistula between the carotid artery and the jugular vein, of thirty-two years' duration, he observed such changes in the absence of vascular disease elsewhere.

Callander,[15] in a study of a large number of arteriovenous fistulas, observed ever-increasing dilatation of the vein about a fistulous communication, which he also attributed to the rise of blood pressure due to the passage of arterial blood through the sac.

Kaufmann [16] reported sclerotic changes in the walls of varicose veins. Benda [17] recorded similar observations and noted intimal thickening from the presence of fibrous tissue, muscular atrophy, new formation of elastic tissue and connective tissue infiltration within and between the muscle bundles of the media of veins.

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11. Lossen, J.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **13**:753, 1904.

12. McIndoe, A. H.: Arch. Path. **5**:23, 1928.

13. Carrel, A.: Technique and Remote Results of Vascular Anastomoses, Studies of the Rockefeller Institute, 1912, vol. 15, no. 27; J. A. M. A. **51**:1662, 1908.

14. Reid, M. R.: Am. J. Surg. **14**:17, 1931.

15. Callander, C. L.: Johns Hopkins Hosp. Rep. **19**:260, 1920.

16. Kaufmann, E.: Lehrbuch der speziellen pathologischen Anatomie, Berlin, W. de Gruyter & Co., 1922.

17. Benda, C., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2.

Elias and Feller,[18] at postmortem examination of the hepatic veins of human beings, confirmed a contractile mechanism which is of far-reaching importance in the dynamics of heart failure. They observed different responses of the hepatic veins according to whether the solution injected was hot or cold, slow-cooling or fast-cooling and thin or viscid. Histologically, such changes in a hepatic vein were found to be due to an accumulation of smooth muscle in the media, especially at the termination of the vein, which contracted in response to heat. They further observed that an increase of pressure in the right auricle causes greater obstruction to the hepatic veins than even in the inferior vena cava. The flow in the left hepatic vein, because of its peculiar origin, may actually come to a standstill from distention.

Mautner and Pick [19] demonstrated experimentally that the liver is an important organ in regulating the quantity of fluid returned to the heart. Contraction of the veins of the liver is a factor in determining the degree of filling of the right auricle and, therefore, in varying the filling of the right ventricle and the stroke volume output of the heart. Mautner and Cori [20] noted further that the opening and closure of the veins of the liver varied with the supply of fluid to the liver. Mautner [21] showed that the contraction of the hepatic veins is of great importance in the circulation. Vagal stimulation in the cat and dog caused closure of the hepatic veins, and the volume of the liver was dependent on the state of arterial filling. On the other hand, stimulation of the sympathetic nerves caused shrinkage of the liver by opening the veins of the organ.

ANALYSIS OF MATERIAL

The inferior vena cava was examined, and the hepatic veins were traced to their terminal branches. Material for study was regularly taken from the inferior vena cava, the right and left hepatic veins and the smaller branches of the right, left and quadrate lobes of the liver.

Macroscopic Changes.—Thickening with deposition of raised yellowish plaques was observed in the intima of the inferior vena cava. There were also dilatation of the right and left hepatic veins, thickening of their walls and deposition of plaques or longitudinal fibrous streaks. The most marked changes were present in the upper two thirds of the veins, especially close to the junctions of these veins with the inferior vena cava. The smaller the caliber of the vein the less marked was the fibrosis, although fibrous streaking was frequently

18. Elias, H., and Feller, A.: Stauungstypen bei Kreislaufstoerungen, Berlin, Julius Springer, 1926.

19. Mautner, H., and Pick, E.: Arch. f. exper. Path. u. Pharmakol. **142**: 271, 1929.

20. Mautner, H., and Cori, G.: Klin. Wchnschr. **1**:1523, 1922.

21. Mautner, H.: Monatschr. f. Kinderh. **27**:385, 1923-1924.

visible to the terminal ramifications. At times a large elevated plaque was seen near the termination of a vein, and sclerosis was more marked at such a site than at the origin of the hepatic veins. The other gross changes in the liver were those characteristic of chronic passive congestion. The portal vein was not investigated in this study.

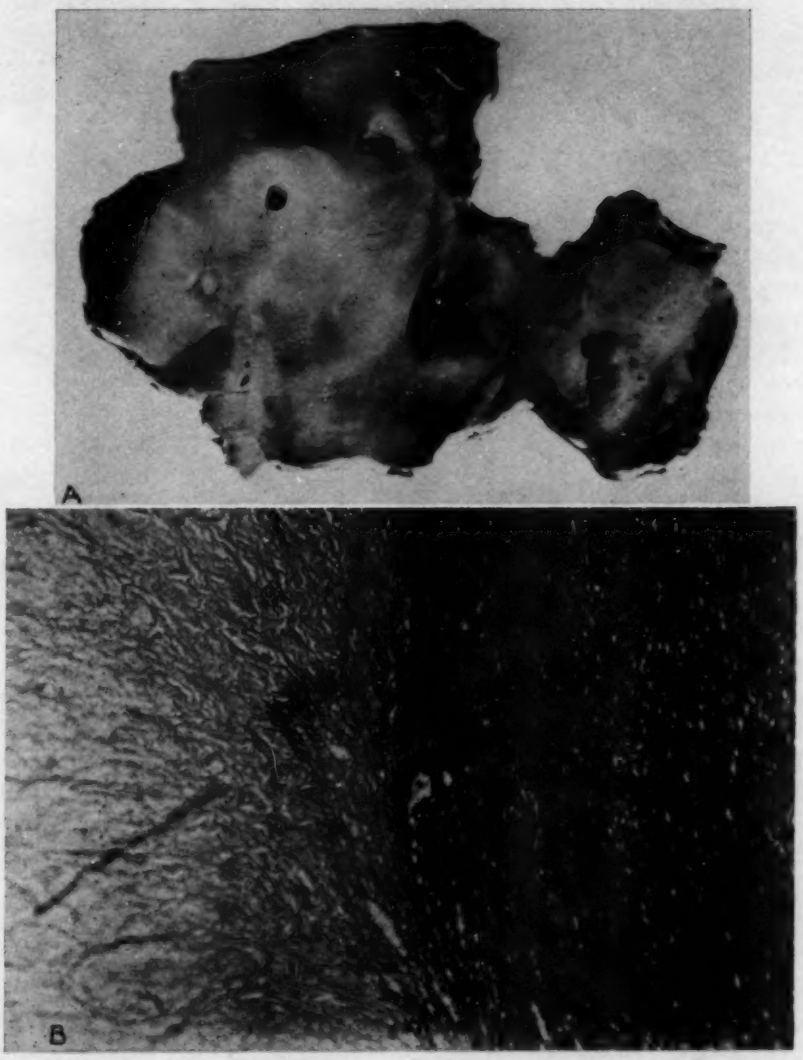

Fig. 1.—*A*, sclerosis of the inferior vena cava and near the ostia of the right and left hepatic veins of a woman of 23 with rheumatic heart disease and advanced congestive heart failure. *B*, enormous hypertrophy in the intima and marked muscular hypertrophy in the media of the inferior vena cava of a woman of 22 with rheumatic heart disease and advanced congestive heart failure; reduced from × 100.

Microscopic Changes.—Sections were stained with hematoxylin-

Inferior Vena Cava: The intima was frequently well preserved and most commonly considerably or greatly hypertrophied. This hypertrophy

eosin, Van Gieson's and Verhoeff's stains.

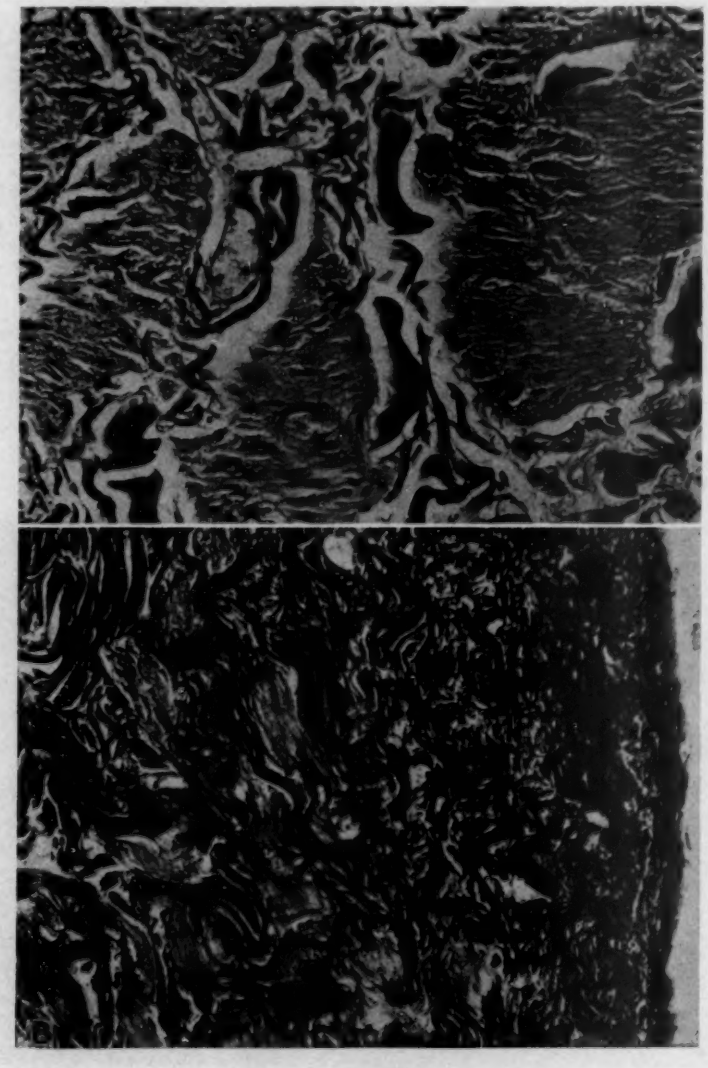

Fig. 2.—*A*, marked muscular hypertrophy in the inferior vena cava of a woman of 26 with rheumatic heart disease and advanced congestive heart failure; reduced from × 240. *B*, enlarged media showing marked muscular hypertrophy and muscle fragmentation by extensive connective tissue ingrowth in a man of 23 with pulmonary tuberculosis and failure of the right side of the heart; reduced from × 240.

was frequently roughly proportional to medial muscular hypertrophy. Fragmentation was commonly encountered. Increases in elastic tissue and muscle cells were common.

The most marked intimal hypertrophy was encountered in the inferior vena cava and at the origin of the right and left hepatic veins. The elastic tissue and the smooth muscle elements were increased. The hypertrophy of the intima was usually proportional to the hypertrophy of the circular and longitudinal smooth muscle in the media. The subintimal layer was frequently enlarged by an ingrowth of elastic tissue.

The media showed striking changes. These were most marked in the inferior vena cava, the vessel in which the muscular layer is best developed. Both the longitudinal and the circular smooth muscle layers were markedly hypertrophied. In fact, the enormous muscular hypertrophy in the media of this vessel was the most significant observation in well marked cases of chronic congestive heart failure. As stated, muscular hypertrophy in the media roughly paralleled intimal hypertrophy.

The muscle cells showed degeneration to various degrees. In some instances, they were large and well preserved; in others, especially if the congestive failure was advanced, various degenerative changes were observed, namely, fragmentation of the muscles, absence of nuclei and hyalinization. Fragmentation was marked, and there was an ingrowth of connective and elastic tissue. There was marked hyperplasia of the fibrous connective tissue which was seen to surround groups of muscle cells or even single muscle fibers. In section, an area of hypertrophied muscle would be seen to taper off so that there were only remnants of degenerated muscle, fragmented by a bizarre ingrowth of connective tissue. Practically complete replacement of muscle tissue by connective and elastic tissue was frequently seen.

Right and Left Hepatic Veins: The changes were similar both macroscopically and microscopically to those in the inferior vena cava, especially in the first portions of these veins. Plaques, scars and fibrous streaking were observed.

Histologically, the intima showed great thickening from elastic tissue ingrowth and muscular hypertrophy. The intimal thickening was not uniform; when it was marked, the lumen of the vessel was encroached on. The subintimal layer was increased in width.

The media showed muscular hypertrophy. The elastic tissue in some instances was replaced by muscular hypertrophy. Where degeneration was marked, the muscle was replaced by connective and elastic tissue and there was marked irregular diffuse fragmentation with connective tissue replacement of muscle cells. Indeed, in some cases mere traces of muscle were frequently seen, and in others muscle was practically absent.

The adventitia was thickened and the elastic tissue increased. Unlike arteriosclerosis, phlebosclerosis was not marked by fatty changes and calcium deposition.

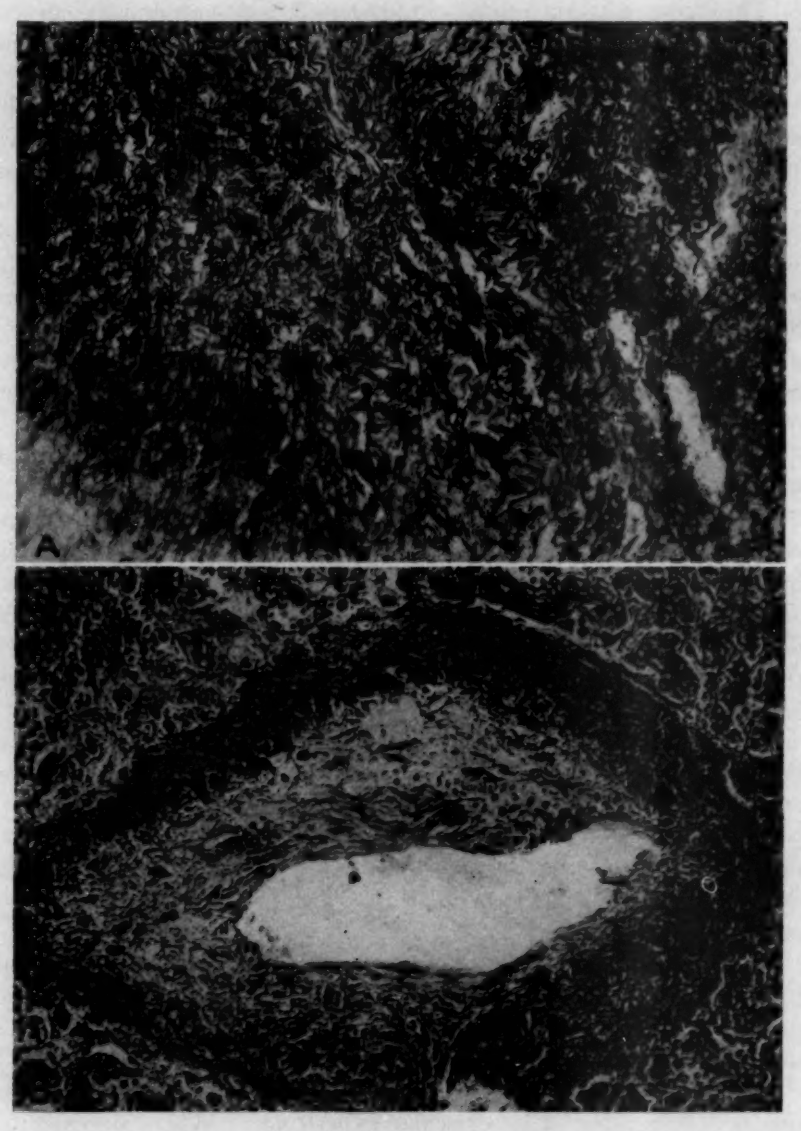

Fig. 3.—*A*, elastic tissue overgrowth associated with marked muscle fragmentation and replacement fibrosis in the inferior vena cava of a man of 53 with chronic hypertensive cardiac failure; reduced from × 200. *B*, a small hepatic vein with increase in the width of the intima and muscular hypertrophy in the media from a man of 25 with rheumatic heart disease and advanced congestive heart failure; reduced from × 240.

Small Branches of Hepatic Veins: The smallest branches of the right and left hepatic veins were especially interesting. They showed persistence of the aforementioned changes, in some instances into the smallest veins, indicating a generalized physiologic state of hypertension in the venous system of the liver.

The intima was hypertrophied; the muscle elements, increased. When the muscle had disappeared, the elastica was sometimes increased. The presence of a large muscularis in the media of a small vein or a large media containing a preponderance of connective tissue, which had replaced the muscle, was indicative of a physiologic response of the media to increased tension. The disparity in some veins, between their size and their muscularis, was striking. In other veins the presence of a large intima with practically no muscle tissue in the media suggested that there had been muscular hypertrophy, which had been replaced. In some instances the outstanding feature in addition to muscular hypertrophy was the connective tissue ingrowth.

The adventitia of the smaller veins showed no striking features. Edema, swelling of the interstitial cement substance and increase in the nuclear elements were often encountered.

An interesting histologic observation was the localized accumulation or heaping up of smooth muscle on opposite sides of the wall of a vein and, between these collections of muscle elements, a peculiar invagination of the wall containing strikingly little muscle tissue. These accumulations of muscle caused marked narrowing of the lumen.

The existence of a similar histologic structure in the adrenal veins was recorded by Lichtwitz,[22] who felt that these accumulations of longitudinal smooth muscle cells constituted a contractile mechanism of the central veins, governed by the sympathetic nervous system, by means of which the discharge of epinephrine into the systemic circulation was controlled. These observations were subsequently confirmed by Kutschera-Aichbergen [23] and Henderson.[24] The latter showed that when two veins each of which has only one longitudinal muscle bundle approach a point of anastomosis, these bundles occur at adjacent sides of the vessels, and when the vessels unite the muscles fuse in the angle of anastomosis. Contraction of the muscles results in active dilatation of the veins.

A review of the literature did not show elsewhere a description of this histologic picture of the hepatic veins.

Though the nerve fibers were not especially studied, nevertheless several unusual findings were encountered, to which I wish to call

22. Lichtwitz, L.: Deutsches Arch. f. klin. Med. **94**:567, 1908.
23. Kutschera-Aichbergen, H.: Frankfurt. Ztschr. f. Path. **28**:262, 1922.
24. Henderson, E. F.: Anat. Rec. **36**:69, 1927.

attention. The nerve fibers were very numerous about the peripheries of the veins and frequently were observed actually in the walls of the veins. The adjacent artery, however, showed either very few or no nerve fibers. This fact leads me to think that the inferior vena cava and

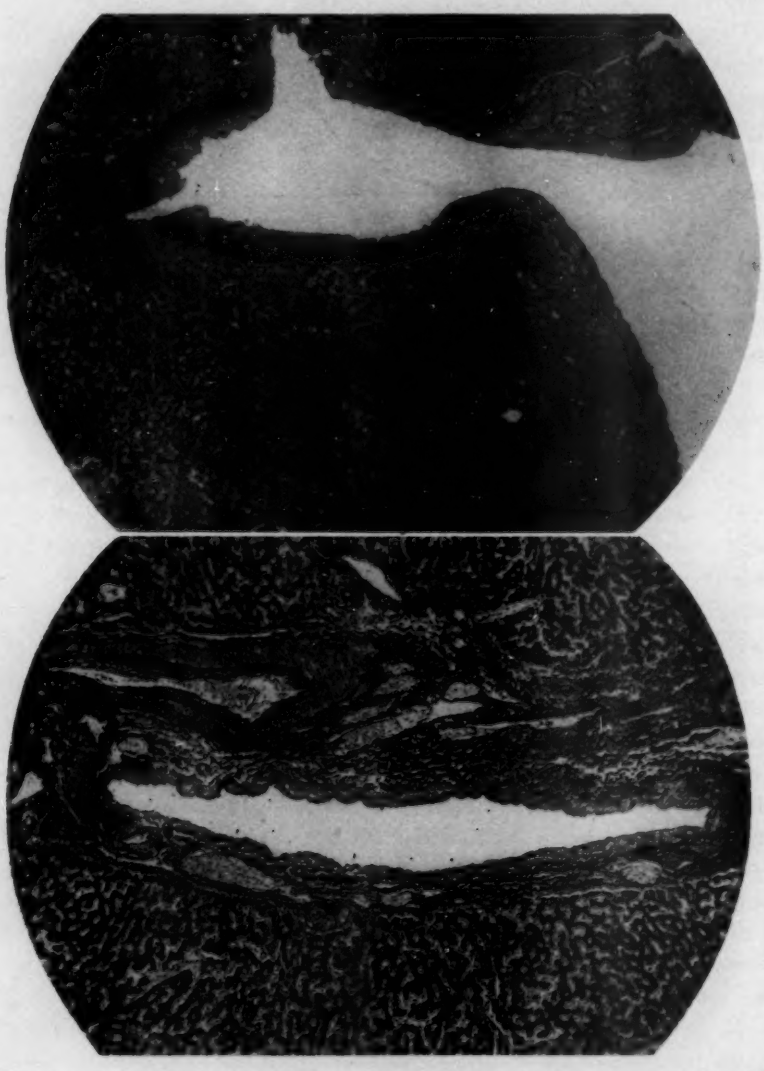

Fig. 4.—*A*, localized accumulation of smooth muscle tissue on opposite sides of an invaginated area in a small branch of a hepatic vein from a woman of 22 with congestive heart failure of long duration secondary to rheumatic heart disease; reduced from × 100. *B*, numerous nerve fibers around and in the wall of a hepatic vein of a 39 year old man with rheumatic heart disease and chronic congestive heart failure; the nerve fibers around the artery are less numerous; reduced from × 60.

hepatic veins have a contractile function governed by the autonomic nervous system. It has been established that such a mechanism may play a rôle in the dynamics of the circulation and that its loss may seriously impair circulatory efficiency. Further study of the rôle of the nervous supply of the hepatic veins in congestive heart failure is now in progress.

The rôle of the elastica was particularly interesting. In slides showing muscle hypertrophy without replacement fibrosis, this enlargement appeared to be at the expense of the elastica. However, in others showing muscle degeneration and replacement fibrosis, the elastic tissue was definitely increased. The question arises whether this elastic tissue ingrowth is compensatory for muscle degeneration.

The rôle of aging in the development of phlebosclerosis may be a significant one. In the cases of advanced congestive failure, degenerative changes and muscular hypertrophy were marked in the hepatic veins. If age is a factor, it is reasonable to expect that the most advanced changes will be found in cases of heart failure, for instance hypertensive heart failure, at or beyond middle life. My observations lead me to believe that the most advanced changes do occur in such cases.

In retrospect it seems that, as a physiologic response to increased work, the walls of the hepatic veins undergo hypertrophy. Furthermore, from persistently increased tension on the walls of the veins and nutritional insufficiency, degenerative changes and replacement fibrosis take place.

COMMENT

Increased intravascular tension whether due to hypertension in the greater or in the lesser circulation has been looked on as the outstanding cause of arteriosclerosis if metabolic disorders are excluded. In the veins, increased pressure or venous hypertension appears to cause a similar though entirely independent process. The infrequency of pulmonary arteriosclerosis as compared with aortic sclerosis and the even greater infrequency of sclerosis of the venous side of the circulatory system as compared with the arterial argue for, rather than against, localized increase in intravascular pressure as the cause of vascular sclerosis. The fact that the tension in the veins is usually at or below zero and that only under exceptional circumstances is it raised above zero is well established. Furthermore, the fact that in cases in which the venous pressure is increased phlebosclerosis is also found favors the view that vascular sclerosis is due to increased intravascular tension. The relative frequencies of aortic and pulmonic arteriosclerosis and of phlebosclerosis may thus be explained.

Sclerosis of the pulmonary artery and veins and of their branches has been shown to occur in cases of failure of the right side of the

heart. In these instances the liver is enlarged and acts as a safety valve for the overloaded lungs. The hepatic veins suffer particularly since, when the heart is in failure, these veins are chronically distended from overfilling. The intrahepatic intravenous pressure is chronically greatly increased. With persistence of congestive failure there is dilatation of the central veins and capillaries, followed by atrophy of the hepatic cells and eventually by replacement fibrosis. As is the pulmonary arterial and venous sclerosis associated with pulmonary hypertension and the vascular sclerosis in arteriovenous aneurysm, in those conditions in which tension of the hepatic veins is for a long time increased, as in Banti's disease, portal cirrhosis and chronic heart failure, the incidence of sclerosis of the hepatic veins is very high. The similarity in causative mechanism between phlebosclerosis and arteriosclerosis is so striking as to lead us to believe that increased intravascular pressure is in many cases the common cause.

A contractile mechanism in the veins of the liver governed by the nervous system has been demonstrated. This mechanism is of great clinical importance if the work of Elias and Feller and of Mautner and his associates is considered. The former demonstrated important influences of enlargement of the right side of the heart on the hepatic veins. The latter showed significant effects on the veins of the liver from disturbances in water metabolism. The loss of this mechanism may be very important in bringing on disturbances in the filling and emptying of the liver conducive to the development and perpetuation of congestive heart failure.

The histologic picture of the veins suggests that secondary to chronic hypertension in the hepatic veins due to failure of the right side of the heart increased physiologic work results in hypertrophy of all the coats of the veins, especially of the muscular layer, most marked in the media. However, with persistence of increased intravenous tension and impaired nutrition, the wall weakens from fragmentation of the muscular layer by an ingrowth of connective tissue. The marked increase in elastic tissue at the time the muscle is breaking down or has largely disappeared may be compensatory.

SUMMARY AND CONCLUSIONS

The mechanical factor responsible for the development of phlebosclerosis is the same as in many instances of arteriosclerosis, namely, prolonged increase of intravascular pressure. Phlebosclerosis and arteriosclerosis are in many ways similar in pathogenesis and morbid anatomy. There is no reason to believe, however, that they are both a part of a widespread vascular disease.

Sclerosis occurs in all the hepatic veins and in the inferior vena cava in congestive heart failure. It is marked in the larger veins, where

there may be thickening of the walls and deposition of plaques. In the smaller veins fibrous streaking is the outstanding feature.

Histologically, the process represents largely a hypertrophic vascular lesion, most marked in the intima and media, secondary to increased work, followed eventually by degeneration and replacement fibrosis from increased vascular tension and impaired nutrition. Likewise in other conditions associated with chronically increased intravenous pressure in the liver, such as arteriovenous aneurysm, varicose veins, Banti's syndrome and portal cirrhosis, hypertrophy and finally degenerative changes occur in the hepatic veins.

Localized accumulations of smooth muscle were observed in the wall of the vein, on oppoiste sides, with marked narrowing of the lumen. Though such a histologic observation has been recorded as made in the adrenal veins, to our knowledge such an anatomic description of the hepatic veins has not appeared elsewhere.

The elastica plays a significant rôle. While diminished in the early muscular hypertrophy, in sections showing advanced muscle fragmentation and degeneration, it was increased. The possibility that this increase represents a compensatory phenomenon secondary to destruction of muscle must be considered.

LIPOID PNEUMONIA OF THE ADULT TYPE (PARAFFINOMA OF THE LUNG)

REPORT OF FIVE CASES

KANO IKEDA, M.D.
ST. PAUL

Within the past ten years, lipoid pneumonia (lipoid cell pneumonia, Goodwin;[1] oil aspiration pneumonia, Ikeda;[2] oil pneumonia, Hayes and Gardner[3]) has come to be recognized as a clinicopathologic entity in the etiology of which aspiration of oily substances plays a dominant rôle. First observed in man by Laughlen[4] in 1925, the condition has since been reported chiefly among debilitated infants.[5] However, during the year 1936 more than 20 cases in adults were reported, indicating definitely that lipoid pneumonia is no longer a rare occurrence among older persons. The condition is a proliferative inflammation of the lung, leading to the development of a peculiar pneumonia, characteristic in its histologic and clinical behavior. (The term "lipoid pneumonia" should be strictly confined to the designation of productive inflammation of the lung in which the fundamental histologic alterations are directly attributable to the presence of foreign oil or fat. The mere demonstration of a few oil-laden macrophages and oil globules due to agonal or terminal aspiration in acute exudative or septic pneumonia is not the criterion of this condition.)

From the Pathological Laboratory of the Charles T. Miller Hospital, St. Paul, and the Department of Pathology, University of Minnesota, Minneapolis.

1. Goodwin, T. C.: Am. J. Dis. Child. **48**:309, 1934.

2. Ikeda, K.: Am. J. Clin. Path. **5**:89, 1935; Am. J. Dis. Child. **49**:985, 1935.

3. Hayes, J. N., and Gardner, L.: Tr. Am. Climat. & Clin. A. **59**:192, 1934.

4. Laughlen, G. F.: Am. J. Path. **1**:407, 1925.

5. (*a*) Pinkerton, Henry: Am. J. Dis. Child. **33**:259, 1927. (*b*) Brunning, cited by Meursing.[11] (*c*) Pollack, B. S., and Potter, B. P.: J. M. Soc. New Jersey **29**: 898, 1932. (*d*) Pierson, J. W.: Am. J. Roentgenol. **27**:572, 1932; J. A. M. A. **99**:1163, 1932. (*e*) Goodwin.[1] (*f*) Rabinovitch, J., and Lederer, M.: Arch. Path. **17**:160, 1934. (*g*) Grayzel, D. M., and Du Mortier, J. J.: Yale J. Biol. & Med. **6**:599, 1934. (*h*) Cannon, P. R.: Tr. Chicago Path. Soc. **14**:219, 1935. (*i*) Ikeda.[2] (*j*) Langdon, John: Rhode Island M. J. **18**:65, 1935. (*k*) Garrison, H. F.: South. M. J. **28**: 322, 1935. (*l*) Graef, I.: Am. J. Path. **9**:862, 1935. (*m*) Baumgartner, Leone, and Angevine, D. M.: Am. J. M. Sc. **192**:252, 1936. (*n*) Holt, L. E., and Howland, J.: Diseases of Infancy and Childhood, ed. 10, New York, D. Appleton-Century Company, Inc., 1933, p. 464.

Lipoid pneumonia occurs in any period of life, more frequently at both extremes of life and particularly in early infancy.

In one of my previous publications on this subject, I said that "the etiologic factors concerned in those cases in adults as well as those in older children are often such that the cases may well be considered in a separate group. . . ." This view has been shared by Houck [6] in his recent publication. Consequently, it is believed that there exists a distinctive type of lipoid pneumonia which, occurring almost exclusively in adults as more or less localized, slowly developing granulomatous or interstitial inflammation, may develop into a permanent lesion of sufficient proportions to provoke eventually serious respiratory embarrassment. The important features of this type of lipoid pneumonia as distinguished from the usual type are found, not in the nature of the essential underlying pathologic process, but in the etiologic factors concerned in its development, such as the amount of the oil, the manner and duration of its administration, its biochemical nature and the character of the local inflammatory reaction induced by its presence. In accordance with this conception, I propose to classify lipoid pneumonia into two types, each with clinicopathologic characteristics which distinguish it from the other.

TYPES OF LIPOID PNEUMONIA

Infantile Type.—The victims are chiefly infants, but the involvement is by no means uncommon among debilitated children and adults. The etiologic agents include those oils and fats which are in common use, such as cod liver oil, milk, liquid petrolatum and its various medicated forms, and others. The condition usually develops under circumstances beyond the control of the patient, namely, forced feeding, regurgitation due to central or local interference (laryngeal paralysis, esophageal obstruction, cardiospasm, tracheo-esophageal fistula), and mentally disturbed or comatose states in which artificial administration of foods and drugs is resorted to. Also, it may follow self-administration of nasal oil in various forms. Clinically, the condition is a slowly developing, low grade pneumonitis with mild respiratory symptoms that show periodic exacerbation due to secondary infection or exudative pneumonia. Early recognized, the process may readily undergo resolution. Essentially there is interstitial proliferative inflammation, not infrequently combined with exudative pneumonia, the latter often being due to the chemical irritation of the oil and to the debilitated condition of the patient which favors bacterial invasion.

6. Houck, G. H., in Medical Papers Dedicated to Henry Asbury Christian, Baltimore, Waverly Press, Inc., 1936, p. 463.

Adult Type.—This occurs usually among older and aged persons, as a result of habitual self-administration of oil, in large total amounts, in the nasal or oral passage for a prolonged period, and occasionally also as a result of direct intratracheal instillation. Rarely, repeated aspiration incident with neurogenic or mechanical interference to swallowing from various causes may be the factor. The only etiologic agents concerned are liquid petrolatum and its numerous medicated preparations. The condition is decidedly chronic, often extending over a period of years. Clinically and roentgenologically, a typical lesion may be interpreted as chronic granulomatous pneumonitis, unresolved pneumonia or a primary or metastatic tumor. Pathologically, it represents a late stage of granulomatous productive inflammation; it is often clearly localized, densely fibrous and neoplastic in appearance—a veritable paraffinoma.

Let it be clearly reiterated here that the pathogenesis of lipoid pneumonia of the adult type is fundamentally the same as that of the infantile type. There are doubtless cases among infants and children as well as among adults which may be best recognized as representing an intermediate stage of the condition.

It is not within the scope of this paper to review the literature dealing with the researches on the reactions of the lung to the intratracheal instillation of medicated oils in chronic pulmonary tuberculosis and other chronic diseases or to discuss in detail the characteristic features of infantile lipoid pneumonia; nor is it my intention to dwell on the distinctive behaviors of oils of animal, vegetable and mineral origins in the pulmonary parenchyma in animals or in man—all of which are fully treated in previous publications by Pinkerton,[7] Ikeda [2] and others.

It is my purpose to demonstrate that lipoid pneumonia of the adult type as here defined is a distinct clinicopathologic entity, to be distinguished from the infantile type. This is believed to be a timely attempt, amply justified by the results of an analysis of the reported cases, coupled with a study of my own cases in adults, in the light of my recent experience with cases of infantile lipoid pneumonia.[2]

STATISTICAL SUMMARY OF CASES REPORTED

I have been able to find 106 cases of lipoid pneumonia recorded in the literature by twenty-four authors in the ten years from July 1925 to April 1936. (Two or three cases were reported twice by two different authors.) Of these cases 68 (64.1 per cent) were in infants and children up to 7 years of age with the single exception of a girl 17 years of age, and 38 (35.9 per cent), in adults. Of the adults, 37 were known to have used liquid petrolatum or its various forms; 14, orally or as a

7. Pinkerton, Henry: Arch. Path. **5**:380, 1928.

laxative; 15, intranasally as drops, sprays, packs or douches, sometimes as a gargle, and 6, intratracheally. Of the adults, 22 came to autopsy. Among these, 8 are considered to have had the adult type of lipoid pneumonia on the basis of the observations at necropsy. Of 16 adults who were not examined postmortem but only clinically, 7 can be classed as having the adult type on the basis of the history and roentgen findings. There were 15 cases of lipoid pneumonia of the adult type, which is 39.5 per cent of all cases of lipoid pneumonia in adults reported. Of these, 11 occurred in males and 4 in females. The ages ranged from 32 to 96, with an average of 58.2 years (average for females, 57 years; that for males, 58.6 years). Of these patients, 6 practiced nasal application; 6 had experienced direct intratracheal aspiration; 2 had received oral administration of oil as a laxative, and 2 did not disclose how the oil entered. The periods of introduction of oil in the cases in which they were recorded were two, four, seven, nine, ten, twenty and "many" years.

From this brief summary, it may be pointed out that (1) there is increasing incidence of lipoid pneumonia of both types in adults, 21 of the 38 cases in adults having been reported within the last year of the period under survey—18 of the infantile and 3 of the adult type; (2) liquid petrolatum is practically the sole etiologic agent; (3) only in 14 per cent of the total number of reported cases, or 39.5 per cent of the cases in adults, was the condition recognized as lipoid pneumonia of the adult type; (4) in these cases males predominated 3 to 1 over females; (5) the condition usually occurs in the fifth decade or later; (6) application of oil in the upper air passage as drops, spray, etc., and direct intratracheal instillation are the most prevalent modes of aspiration, and (7) aspiration over a period of years is an important etiologic factor.

REVIEW OF CASES OF ADULT TYPE REPORTED

The first case of lipoid pneumonia in adults was reported in 1925 by Laughlen.[4] It occurred in a paralytic patient 37 years of age who was given 1½ ounces (45 Gm.) of liquid petrolatum three times daily for four and a half months. The patient died of bronchopneumonia. The second case was reported by Thomas and Jewett[8] in the following year, in a man 32 years of age who for four years suffered from cardiospasm and esophageal dilatation and died of mediastinal abscess and aspiration (cream) pneumonia. These two cases are examples of lipoid pneumonia of the infantile type in adults. The first case of lipoid pneumonia of the adult type was reported in 1933 by Fischer-Wasels[9] as

8. Thomas, W. S., and Jewett, C. H.: Clifton M. Bull. **12**:130, 1926.
9. Fischer-Wasels, B.: Frankfurt. Ztschr. f. Path. **44**:412, 1933.

one of pulmonary contraction due to aspiration of liquid petrolatum. He ignored the prior publications in America by Laughlen, Thomas and Jewett, Pinkerton and Pierson, none of whom observed large fibrous tumor-like masses in the lungs such as he encountered. The patient was a woman of 70 years who was suffering from coronary disease. The roentgenograms of her chest revealed a large tumor-like shadow along each of the pulmonary roots, extending down into the lower fields. Radiotherapy failed to reduce the size of the shadows. At necropsy, firm nodules were palpated at the hilus of each lung. The lower lobes were collapsed and revealed cicatricial contraction. From 100 to 120 Gm. of liquid petrolatum were recovered from both lungs. It was brought out that the patient, who was a victim of recurrent respiratory infection, had for more than twenty years been in the habit of instilling menthol in oil into her nose.

Another case was reported later in the same year by Bodmer and Kallos [10] as the first and only case of pulmonary cirrhosis in which the etiologic significance of liquid petrolatum was recognized clinically. The patient, a man 52 years of age, had suffered for eleven years from laryngeal pachydermia and catarrhal infection. Every evening for ten years he introduced into both nostrils from 50 to 100 cc. of liquid petrolatum and during the procedure intentionally aspirated the oil regularly in order to lubricate the vocal cords. The roentgenograms taken six years after the onset of illness showed a well defined shadow about the size of an apple in the left lower field. A similar shadow appeared later in the right lower field. On the basis of the history, a clinical diagnosis of pulmonary cirrhosis due to the aspiration of liquid petrolatum was finally made.

In the same year, 2 cases of "pneumonoliposis" in elderly people were reported by Meursing.[11] One of these presented at necropsy a chronic granulomatous lesion characterized by areas of fibrosis, lipophages, giant cells and high cuboid alveolar lining cells.

In 1934, Ellinger [12] reported 3 adult cases of "indurating pulmonary condensation" following intratracheal aspiration of liquid petrolatum, in which the roentgenograms showed diffuse dense shadows in the lower lobes of both lungs. Two of the patients had undergone total laryngectomy for removal of cancer. The patients would fill the tracheotomy tube with paraffin oil to prevent crusting and dryness of the mucosa.

Hayes and Gardner [3] in 1934 reported 2 cases of "oil pneumonia." A woman 32 years of age who had used Mistol (liquid petrolatum containing camphor, eucalyptol, menthol esters and trichlorbutylalcohol)

10. Bodmer, H., and Kallos, P.: Arch. f. Ohren-, Nasen- u. Kehlkopfh. **136**: 40, 1933.

11. Meursing, F.: Nederl. tijdschr. v. geneesk. **77**:3878, 1933.

12. Ellinger, E.: Fortschr. a. d. Geb. d. Röntgenstrahlen **69**:397, 1934.

for ten years as a nasal spray and gargle presented a roentgenogram of the chest showing densities in both lower fields, suggestive of malignant growth or of unresolved pneumonia. At necropsy, the right lung showed organizing pneumonia and the left a large mass of fibrous scar tissue near the hilus. The diagnosis was made a year later when a large amount of oil was seen floating in the preserving fluid. The second case occurred in a man 62 years of age who used "a bottle of Mistol" daily as a nasal spray for a prolonged period. At necropsy, there was a large consolidation composed of firm yellow tissue along the pulmonary roots.

In 1935, I [2] briefly referred to the case of a woman 69 years of age, a victim of paralysis agitans, who at necropsy revealed a localized tumor in the lung, which proved to be lipoid pneumonia of the adult type.

Three cases were reported by Graef [13] in adults in the same year. At least 1 showed macroscopic lesions which were mistaken for tumor metastases "at close examination." In all instances, the aspiration of liquid petrolatum followed its oral administration.

Ball [14] in 1935 reported the case of a man 96 years of age who for many years had used a medicated liquid petrolatum spray for his nose and throat. Necropsy revealed an extensive scarring of the lungs, which was due to quantities of aspirated oil.

Early in 1936, Davis [15] reported 3 cases of lipoid pneumonia of the adult type. A man aged 47 received ten intratracheal instillations of medicated liquid petrolatum, after which he suffered from marked dyspnea and cyanosis with signs of consolidation over the lower lobe of the right lung. For seven years he suffered from severe recurrent pulmonary symptoms, to which he finally succumbed. At necropsy, large portions of both lungs were found to be transformed into fibrous tumor masses. The pathologic aspect of this case was fully discussed by Houck [6] in another article under the title of "pulmonary oil tumors." The second patient, aged 52, packed his nostrils with oil-soaked cotton and practiced frequent self-administration of liquid petrolatum containing menthol and thymol, drawing this into the trachea, while the third used approximately 7 gallons (26 liters) of mineral oil as a nasal douche annually for nine years. All these patients presented masslike shadows in the lungs, which in the light of the history were recognized roentgenologically as those of "oil pneumonia."

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13. Graef, I.: Am. J. Path. **9**:862, 1935; personal communication to the author.

14. Ball, F. E.: Illinois M. J. **69**:62, 1936.

15. Davis, K. S.: Radiology **26**:131, 1936.

Tchertkoff and Ornstein [16] collected 10 cases in which the pulmonary lesions were clinically attributed by them to intranasal instillation of mineral oil. In cases 1, 4 and 6 tumor-like shadows were observed in the roentgenograms, along with the usual peribronchial fibrosis. All of the patients recovered on withdrawal of the intranasal medication.

Ritchie [17] recently reported 9 cases of lipoid pneumonia in adults. All of the patients, however, died early and probably had the infantile type of this condition.

It should be pointed out that more and more of the cases of lipoid pneumonia in adults are being recognized clinically and at necropsy. Curiously, in practically all of them, liquid petrolatum is found to be the etiologic agent. Many of the patients have used it orally as a laxative, particularly those who are the victims of chronic debilitating disease and die of bronchopneumonia (Graef,[13] Ritchie [17]). A few have used it intranasally as a spray or as drops and complain of bronchopulmonary symptoms which disappear with discontinuance of the nasal application (Tchertkoff and Ornstein [16]). In the last 18 cases reported in adults, a clinical picture was presented similar in every respect to that found in infants, the only difference being that in the infants oils and fats other than liquid petrolatum were encountered far more frequently than in adults, principally owing to the common practice of artificial feeding and medication among these babies.

BRIEF CLINICAL CONSIDERATION

As has already been stated, the causative agents of lipoid pneumonia of the adult type are practically limited to liquid petrolatum and its many medicated combinations. The oil may be taken either orally or intranasally. More frequently, it is self-administered, often habitually over a period of years, being dropped or sprayed into the upper air passages. Spraying, since it is more effective, must be regarded as more dangerous. Involuntary aspiration of a part of the oil thus administered into the trachea without exciting the reflex inhibition is a well known phenomenon, amply supported by experimental evidence both in man (Pirie [18]) and in animals (Laughlen,[4] Ikeda [2]). This is said to be further facilitated by the mildly anesthetic effect of such drugs as menthol and thymol on the mucous membrane. In a few instances, direct intratracheal instillation of the oil either by the patient or by the physician has been reported. Repeated accidental aspiration incidental to forced feeding, regurgitation and other mechanical and neurogenic interferences with swallowing has also been responsible but less frequently.

16. Tchertkoff, I. F., and Ornstein, G. G.: Quart. Bull., Sea View Hosp. **1**:139, 1936.

17. Ritchie, G.: Wisconsin M. J. **35**: 286, 1936.

18. Pirie, A. H., in discussion on Pierson.[5d]

Chronic cardiac or pulmonary disease may interfere with the prompt complete disposal of foreign oil and thus favor the continued retention of an increasing amount of the residue in the pulmonary parenchyma, which in turn contributes further toward the development of this condition.

When the condition is accidentally discovered at necropsy, only a vague history referable to pulmonary distress may be obtainable. As a rule, however, the victim suffers from chronic recurrent infection of the upper respiratory tract, for which relief is continuously sought through local treatment. The pulmonary symptoms are essentially the same in all cases, differing only in degrees or in the complications due to secondary infection. Unproductive cough and pain in the chest with periodic recurrence and exacerbation of symptoms are the characteristic features of the disease in the earlier stage. Attacks of severe paroxysmal cough with the production of scanty, mucoid and often blood-streaked sputum are reported. Production of sputum and frank hemoptysis have been recorded in a few instances. Persistence of these symptoms together with a low grade rise in temperature has led to the diagnosis of pulmonary tuberculosis in some cases. Rise in temperature and productive cough depend usually on the presence of secondary infection or pneumonia. Death is usually accounted for by terminal septic pneumonia or other concurrent major condition, notably cardiac failure. The presence of oil globules in the sputum is considered by some authors to be diagnostic. This, however, is not as reliable as might be expected.

ROENTGEN FINDINGS

The roentgenograms of the chest at first may reveal merely heavy bilateral shadows at the hilus and exaggerated linear markings extending into the lower fields, indicating increased fibrosis of the pulmonary roots. Chronic aspiration of oil per se is being recognized as an important factor in the production of these shadows. In the well established cases there is demonstrated a massive shadow or a conglomeration of shadows along the hilus and perihilar areas, extending into the base, sometimes unilaterally but more often bilaterally, with evidence of fibrosis and atelectasis of the surrounding parenchyma. Such conditions as unresolved pneumonia and bronchiectasis have been diagnosed. If uncomplicated by the effects of a superimposed infection, these shadows are likely to be sharply defined and to simulate a neoplasm. The roentgen criteria of bronchogenic carcinoma have been fulfilled in a few reported instances. From the nature of the lesion, it is evident that the uncomplicated roentgen shadow increases in size very slowly. The shadows may vary from time to time, depending on the presence or

absence of secondary exudative inflammation. They may actually decrease in dimensions during the quiescent stage. The shadows in well established cases are permanent and incapable of resolution. This is an important roentgen sign in differentiation between lipoid pneumonia of the adult type and lipoid pneumonia of the infantile type. The latter, unless terminated by death, will eventually undergo resolution. Periodic roentgen examination of the chest is therefore important. The pulmonary lesion in the advanced stage as revealed on the roentgenogram is usually more impressive and striking than would be expected from the clinical signs and symptoms. Nevertheless, the roentgen signs are an important aid in the early clinical diagnosis of this condition, if interpreted in the light of a history positive for the presence of lipoid.

PATHOLOGY

Unlike animal and vegetable oils, liquid petrolatum is chemically inert and acts purely as a foreign body in the pulmonary parenchyma. It is partly eliminated through expectoration and partly removed through the lymphatics by wandering macrophages which phagocytose it. The continued presence in the alveolar recesses of residual oil tends to cause local irritation, which results in low grade productive inflammation analogous to the foreign body reaction. Such medicinal agents as menthol, thymol and ephedrine, which are often employed in combination with liquid petrolatum, are responsible for acute diffuse exudative inflammation apparently because they chemically irritate the lining of the lower respiratory tract. The result is a picture of simple foreign body reaction and acute chemical inflammation combined. The latter apparently subsides spontaneously and often rapidly in the absence of secondary bacterial invasion, the offending agent being readily eliminated by the tissue, which appears to acquire tolerance for it, while the petrolatum continues to act as a foreign body.

The pathologic nature of the adult type of lipoid pneumonia, therefore, is essentially that of a paraffinoma in the lungs in its various stages of development, extending from early nonsuppurative proliferative interstitial pneumonitis to chronic granulomatous foreign body reaction, climaxing, in the final stage, with widespread fibrosis and tumefaction of the involved area.

Lipoid pneumonia of the infantile type, particularly that brought about by liquid petrolatum and its allied preparations, may be regarded as representing the initial stage of the adult type. It is terminated as a rule either in resolution on the withdrawal of the offending agent or in death due to complicating secondary pneumonia, which frequently develops in debilitated infants. On the other hand, in the older patients who continue to receive applications of oil and survive repeated attacks

of secondary pneumonia, the process may continue through intermediate stages to finally fully developed lipoid pneumonia of the adult type. In the early stage the adult type of lipoid pneumonia may tend to be diffuse and even involve an entire lobe. The involved area is light grayish yellow and shows an area of diffuse consolidation of the consistency of dry sponge cake. The pleura is stretched and smooth. The cut surface is dry, granular and finely spongy. No pus is demonstrated, but a small amount of cloudy milky fluid may exude on pressure. Minute droplets of oil are observed to float in the fluid. The gross appearance may suggest lobar pneumonia in the stage of gray hepatization. A small piece from the involved portion of such a lung may float in water because of its oil content. By grinding a few grams of the lung in a few cubic centimeters of water and by centrifugating the supernatant fluid, a layer of oil is readily demonstrated. The low power microscopic view of a typical lesion may be best described as that of a storm-torn spider web; it shows a network of alveoli, many distorted, some collapsed and others emphysematous (fig. 1 *A*). Many alveoli appear as vacuoles of varying dimensions, while others are filled with clusters of large foamy macrophages. The alveolar septums are thickened with edema and connective tissue proliferation and show a few small foci of lymphocytic infiltration. The alveolar lining may be represented by a layer of macrophages of varying shape and size, some extending their pseudopodia into the alveolar space and others, in coalescence, forming multinucleated giant cells of varying dimensions, all more or less vacuolated (fig. 1 *B*). These vacuoles and spaces are literally filled with globules of oil, which also infiltrate into the interstitial areas. Acute infection may so overshadow the underlying lesion that a diagnosis of bronchopneumonia is made. If severe secondary infection develops early or other oils are involved, the process may become more complicated because of the possible development of more lasting lesions in the former instance and the biochemical effects which are entirely foreign to liquid petrolatum in the latter. For example, cod liver oil is known to produce early fibrosis and giant cell formation. It is a most dangerous one of the oils concerned in infantile lipoid pneumonia but has not been reported as the agent in adults.

In its typical form, lipoid pneumonia of the adult type presents itself at necropsy as one or more distinct nodular masses of varying dimensions, located usually in the lower lobe, in proximity to the hilus and along the bronchial trunks. The nodules may be deep seated and easily overlooked. The individual mass is usually sharply demarcated but may merge gradually into the surrounding parenchyma. Sometimes it is casually dismissed as localized fibrosis or chronic pneumonia, and sometimes it is interpreted as a tumor (fig. 2 *A* and *B*). On careful examination, the cut surface of the mass is dry, grayish white and

often tinged with irregular yellowish mottling. It appears to represent a growth of connective tissue fibers and is firm and rubbery in consistency. No pus is demonstrated. A small number of yellowish or milky oil droplets may be expressed. A few small cavities may be encountered. These are filled with oily material. Coexisting septic pneumonia may completely surround and obliterate the primary lesion. Microscopically, the lesion is characterized by chronic granulomatous inflammation in which three cardinal processes are recognized: (1) a diffusely spreading fibroblastic proliferation, which obliterates the usual alveolar framework; (2) equally widespread infiltration by lymphocytes and plasma cells, which are seen in scattered collections and solid masses, and (3) wandering of conspicuous large foamy macrophages in small numbers within the stroma and in irregular masses within the distorted alveoli (figs. 3 *A* and *B*, 4 *A* and 5 *B*). Here, the alveolar lining may become distinctly epithelialized by a layer of cuboid cells (which are, in my opinion, epithelial in origin). In the more fibrous areas, the alveoli are represented by distended rounded spaces surrounded by a thick, densely fibrous, collagenous connective tissue framework. These spaces are filled with oil, which tends to become adherent to the inner lining and often forms a crescent giant cell (fig. 5 *B*). Multinucleated foreign body giant cells are invariably demonstrated. Many of them appear as crescents along the inner lining of distended alveoli and represent undoubtedly coalescence of macrophages caught in adherent drying oil. Others appear as large multinucleated cells of varying proportions, taking an active part in the pathologic process. Polymorphonuclear leukocytes are conspicuous by their absence. Scattered about in the involved areas may be found small pseudotubercle formations. Some of these represent condensed granulomatous lesions scarcely visible to the naked eyes. Others are microscopic and may represent small masses of disintegrating oil, which appears to undergo "organization" (fig. 4 *B*). Still others are perivascular fibrous nodules, which are formed apparently by local fibroblastic proliferation, following stimulation by oil set free in the rupture of distended perivascular lymphatics (fig. 5 *A*). Globules of free oil entrapped in the alveolar spaces may gradually undergo disintegration and become solidified and organized into hyaline fibrous bodies.

These localized tumor-like lesions, typical as they are, may fail to produce serious clinical symptoms, and their discovery at necropsy is in many instances accidental.

When clinical signs and symptoms are definitely referable to the condition, it is likely to involve a large portion of one or both lungs. At necropsy, the lesion appears as a well defined large mass or several nodular areas and may occupy an entire lobe, usually the lower; more often it is present on each side (fig. 2 *D*). It is rubbery in con-

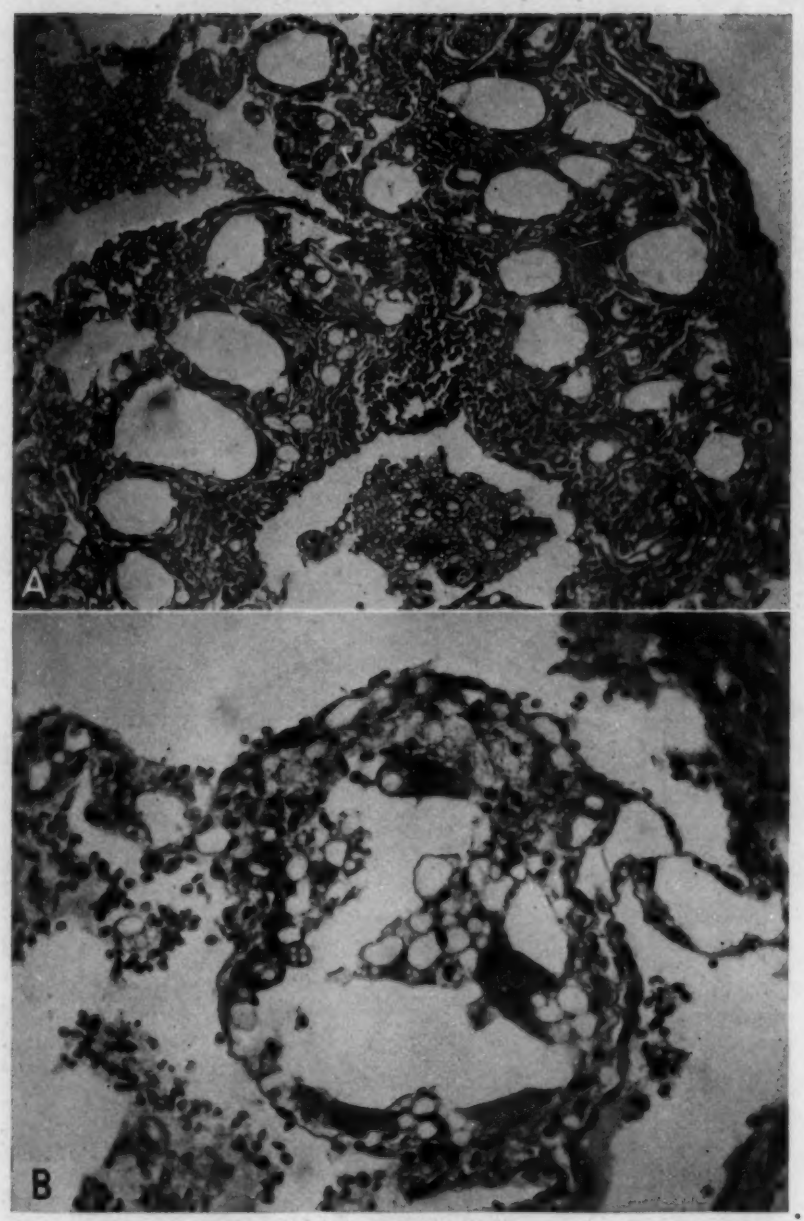

Fig. 1 (case 1).—*A*, general view of a subpleural area showing lipoid pneumonia of the adult type in a relatively early stage. Nearly all the spaces were shown to be filled with aspirated liquid petrolatum. Note the septal interstitial fibrosis, the focus of lymphocytic infiltration, several foreign body giant cells along the alveolar spaces and clumps of oil-laden macrophages in larger spaces; Van Gieson; × 100. *B*, enlarged view of an alveolus showing along its inner lining macrophages and giant cells loaded with globules of oil. Note the oil-laden cells within the surrounding septum; hematoxylin and eosin; × 430.

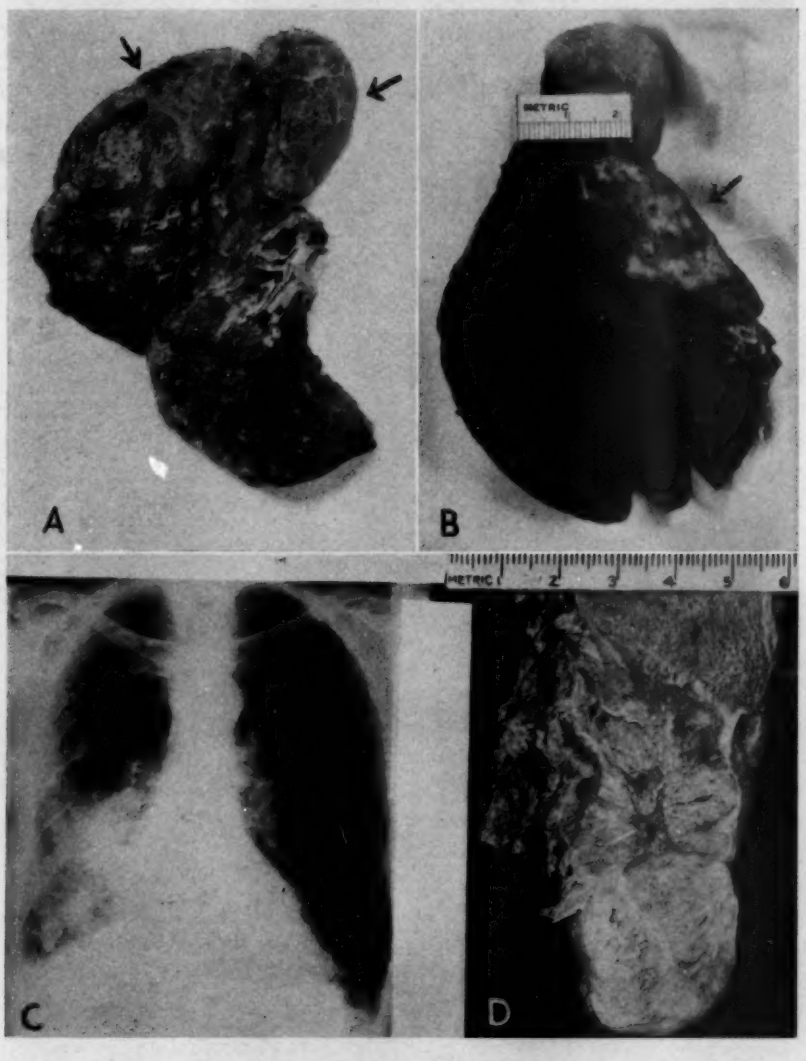

Fig. 2.—*A*, portion of a lung in case 3, showing a localized area of lipoid pneumonia and another less defined area. Note the characteristic spongy apperance of the lesion along with irregular areas of dense fibrosis. *B*, well circumscribed hard tumor-like mass of lipoid pneumonia in case 4, mistaken for metastatic carcinoma—a typical paraffinoma—one of several such nodular tumors in the lung. *C*, roentgenogram of the chest in case 5. The shadow in the right lower lobe was interpreted as probably due to bronchogenic carcinoma. *D*, large tumor-like mass from the right lung shown in figure 2*C*, typical of advanced lipoid pneumonia of the adult type.

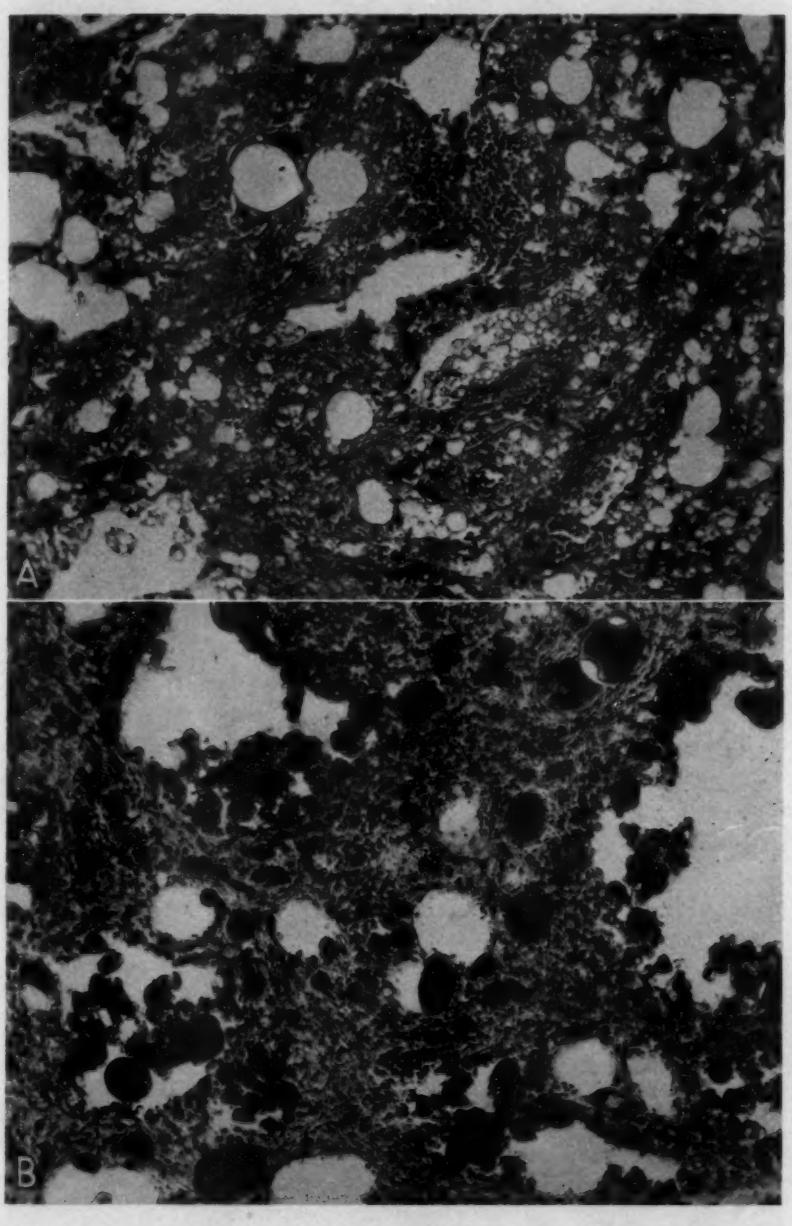

Fig. 3 (case 2).—*A*, view of a typical granulomatous lesion, showing the spreading proliferation of connective tissue fibers, a collection of lymphocytes, nests of foamy macrophages, distorted and isolated alveoli and one giant cell; hematoxylin and eosin; × 100. *B*, section stained with scarlet red, showing numerous globules of oil within alveolar spaces, spreading fibrosis of the stroma with diffuse infiltration by lymphocytes, and one giant cell; scarlet red; × 100.

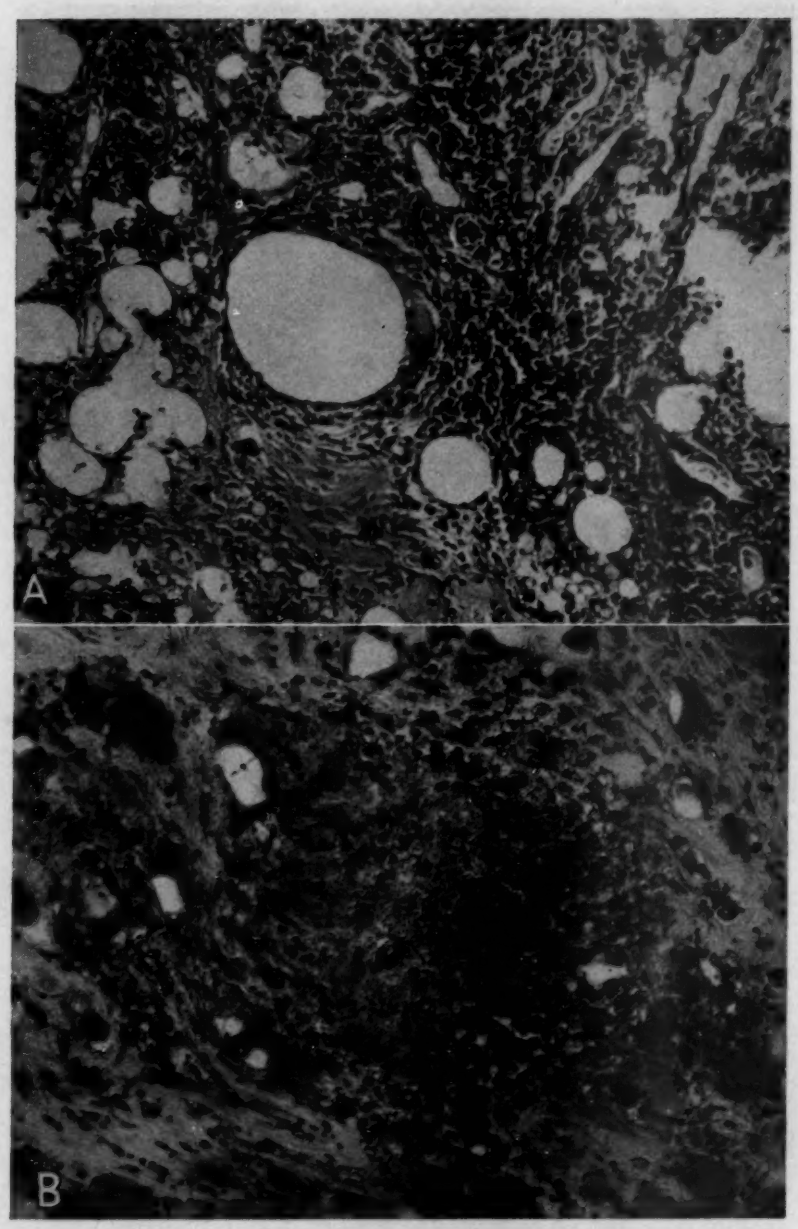

Fig. 4 (case 3).—*A*, view showing a cellular granulomatous area; hematoxylin and eosin; × 100. Note a crescent-shaped giant cell lying firmly against a round solitary alveolar space. The smaller spaces were shown to be filled with oil. *B*, microscopic pseudotubercle composed of a mass of disintegrating old globules of oil undergoing "organization"; scarlet red; × 100.

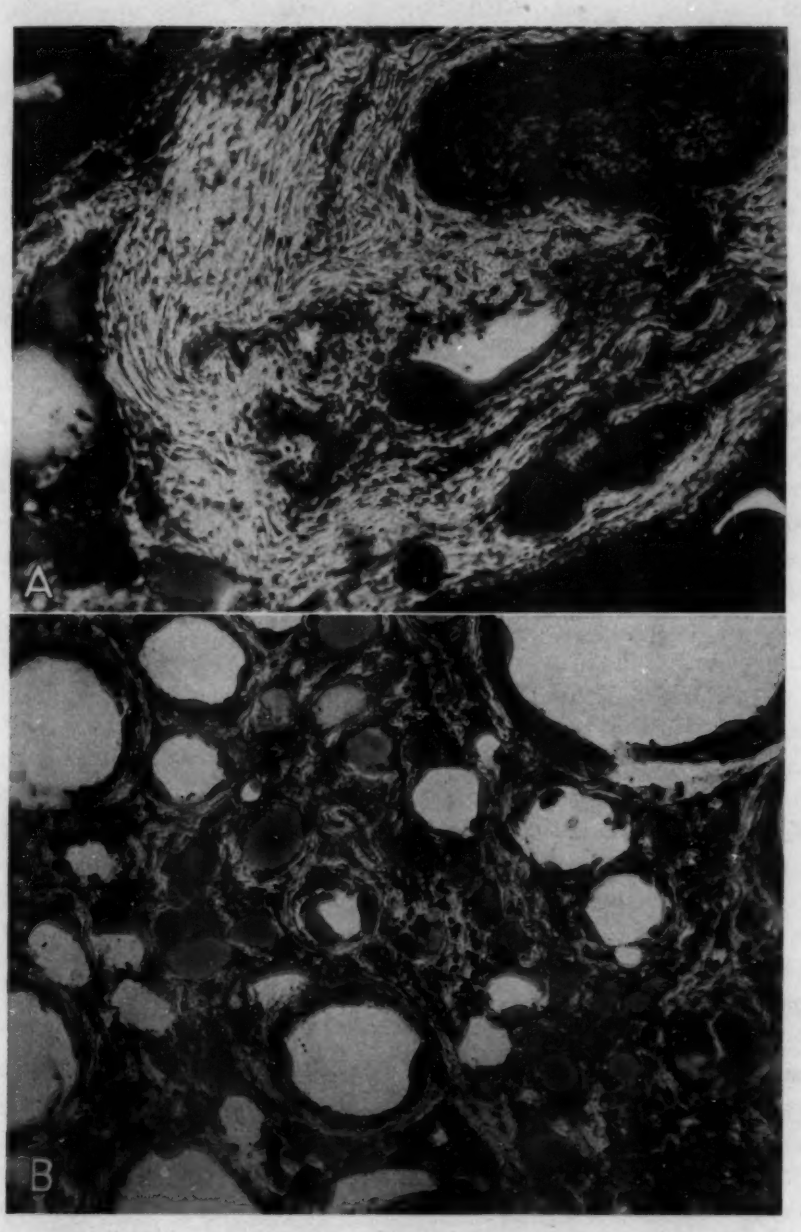

Fig. 5.—*A*, portion of a perivascular pseudotuberculous nodule in case 3, showing thick concentric proliferation of connective tissue fibers around a small vessel (shown in the upper right corner) and a few entrapped globules of oil within distended lymph spaces. Many such globules in various stages of development are present in selected areas; scarlet red; × 75. *B*, view in case 4, showing proliferation of thick collagenous fibers around alveoli, which are rounded and filled with oil. The globule of oil tends to form a crescent along the inner lining of the wall, and in many instances a giant cell forms by the coalescence of macrophages; scarlet red; × 100.

sistency, spongy in areas, grayish white, definitely fibrous and mottled with yellowish streaks. Oily material or free droplets of oil may be expressed from the surface. The adjacent parenchyma may be collapsed and the overlying pleura shrunken and wrinkled or thickened and adherent. The gross appearance of the lesion has led to the diagnosis of chronic granulomatous pneumonitis, lymphogranulomatosis, Hodgkin's disease and metastatic or primary tumor, notably, bronchogenic carcinoma. Microscopically, the fundamental changes are essentially those of the nodular lesion already described. The chief feature is the denseness of the widespread fibrosis in areas, which may appear as a solid connective tissue growth or as a fenestrated fibrous structure in which each space is occupied by a solid globule of oil (fig. 6 *A* and *B*).

The regional lymph nodes may show invasion by the oil. They may be enlarged and definitely fibrous or show small tubercle-like nodules. Microscopically, droplets of oil are scattered freely about along the peripheries of the follicles and in the sinuses. Small globules of oil are ingested by the wandering carbon-laden macrophages scattered through the spaces of the node. Patches of fibrosis may be noted. Granulomatous nodules and pseudotubercles have also been observed.

The identification of liquid petrolatum may be made with reasonable certainty without resorting to chemical analysis. It absorbs in vitro only about 20 per cent (estimated) of scarlet red and therefore reacts to it with a pale orange-yellow color as contrasted with other oils and fats, which are easily saturated by the dye and appear bright orange to deep scarlet. It is negative to osmic acid and Ciaccio stain. Liquid petrolatum, furthermore, has a greater tendency toward fine emulsification. The oil is readily extracted from the tissue by grinding a piece in water in a mortar and subjecting the supernatant fluid to centrifugation.

The occurrence of lipoid pneumonia of the adult type among infants may be possible but is most unlikely. Tumor-like nodules of lipoid pneumonia in infants are as a rule composed of solid masses of oil and oil-laden macrophages in a slightly altered edematous parenchyma. In the lesions of longer standing, they may show a granulomatous process with increased interstitial fibrosis, which may be regarded as an early stage of the adult type of lipoid pneumonia, provided the etiologic agent is definitely proved to be liquid petrolatum.

It should be noted, however, that the lesions representing various stages of development, from the mere collection of foamy oil-laden macrophages within the little altered alveoli to the area of widespread connective tissue proliferation, are usually found in the same lung.

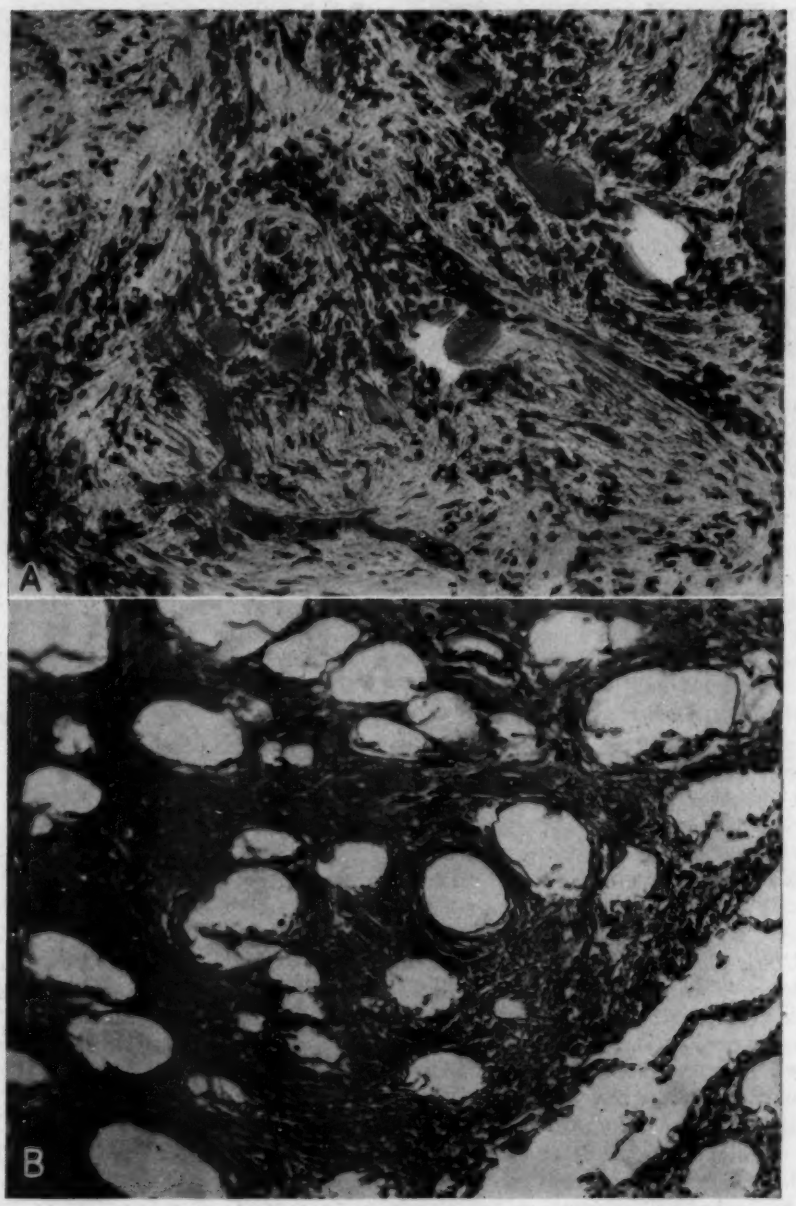

Fig. 6 (case 5).—*A*, more fibrous and cellular (plasma cells) portion of the lesion; scarlet red; × 100. *B*, area showing the periphery of a scantily cellular fibrous mass well demarcated from the surrounding parenchyma; hematoxylin and eosin; × 100.

indicating the existence of a continuous pathologic process in the development of this condition.

REPORT OF CASES

In a series of more than 20,000 necropsies recorded over a period of twenty years prior to 1932 not a single instance of lipoid pneumonia was included. In the fall of 1932, a peculiar pneumonic lesion was accidentally observed during the routine microscopic examination of necropsy sections. This led to the discovery of 7 cases of lipoid pneumonia in a series of 107 consecutive necropsies of infants in a period of three years. I have since been able to collect 5 instances of lipoid pneumonia in adults. These 5 cases form the basis of the present study.

CASE 1.—A white man aged 58 was admitted to the hospital because of periodic hemorrhages from a duodenal ulcer and resulting anemia. Gastro-enterostomy was successfully performed. Two days later the patient began to twitch and breathe heavily and then lost consciousness. He had attacks of cyanosis and hiccupped from time to time. His blood pressure varied, and on several occasions was lowered to 85 systolic and 50 diastolic. The patient began to show physical signs of hypostatic pneumonia and died five days after the operation. The clinical diagnosis was cerebral hemorrhage.

For several days prior to the operation, the patient was given ½ ounce (14 Gm.) of mineral oil twice or three times daily. Occasional vomiting spells were recorded. He had been constipated for a number of years and was in the habit of taking a mild cathartic regularly. No oil was administered either orally or intranasally after the operation.

Necropsy.—The right lung, weighing 1,000 Gm. was fully expanded and voluminous. The pleural surfaces were stretched, shiny and grayish yellow. Crepitation was equally reduced throughout the entire lung. The cut surface was light grayish yellow, comparatively dry and granular and uniformly spongy and rubbery in consistency. Only a small amount of a milky fluid escaped on pressure. The left lung, weighing 800 Gm., was equally voluminous. Crepitation was reduced throughout, and irregular areas of consolidation were disclosed on palpation. The cut surface was dark red, and the parenchyma was saturated with bloody fluid. There were irregular small grayish areas of consolidation, from which droplets of pus exuded. Grossly, the left lung presented a typical picture of bronchopneumonia, while the right lung had an appearance suggestive of lobar pneumonia, the stage of gray hepatization, although the color was definitely yellower and the cut surface considerably drier than was usual for lobar pneumonia in this stage. A piece of the consolidated portion of the lung failed to sink in water owing to the oil it contained.

The microscopic appearance of the right lung was as baffling as it was striking. The picture of conglomerated vacuoles of varying diameters in a loose network of alveolar septums at once suggested the presence of oil or fat (fig. 1*A*). This was readily demonstrated in abundance as globules and droplets filling diffusely many alveolar spaces and septums. Pulmonary fat embolism was suggested because of apparent occlusion of many septal capillaries by columns of oily substance. The latter was pale orange yellow to scarlet red and negative to osmic acid and Ciaccio stain (which ruled out animal and vegetable oils). The

conspicuous presence of giant and multinucleated cells along the alveolar lining (fig. 1*B*) and of macrophages, many of which were filled with emulsified oil, together with the proliferation of septal connective tissue suggested a foreign body reaction. The left lung showed an area of diffuse suppurative inflammation, in which were buried many oil-laden macrophages and giant cells, indicating the preexistence of lipoid pneumonia.

CASE 2.—A woman aged 69 had been confined to bed for the past four or five years, suffering from marked asthma, rigidity and tremor of the body and extremities. Of late, she had become weaker and more rigid and had difficulty in taking nourishment. The blood pressure was 120 systolic and 80 diastolic.

Necropsy.—Arteriosclerotic paralysis agitans was the cardinal diagnosis. The right lung weighed 425 Gm. and the left 520 Gm. There were diffuse hypostasis and terminal bronchopneumonia in the dependent portions of both lungs. There was a firm rubbery consolidation, grayish white and fairly well defined, like a tumor nodule, 5 cm. in diameter, in the lower lobe of the right lung. A small droplet of yellowish green material was expressed from the cut surface on pressure. The nature of this tumor-like mass was identified only after demonstration of a typical microscopic picture of lipoid pneumonia of the adult type.

Subsequent inquiries failed to establish that any oily preparation had been administered either orally or intranasally.

CASE 3.—A white woman aged 68 had a fracture of the neck of the right femur of six weeks' duration. Six years previously she had an obstruction of the nasal passages which necessitated an operation on the septum. The nasal passages were now closed, and there was a perforation of the septum measuring 1.5 cm. in diameter. The patient had been given oil nasally twice daily for a prolonged period. The lungs showed poor expansion but were otherwise normal. The heart had a systolic murmur at the apex and an occasional extrasystole. Death was due to terminal hypostatic bronchopneumonia.

Necropsy.—The pericardial sac was obliterated by firm adhesions. The coronary arteries were slightly atheromatous.

The right lung weighed 452 Gm. There were fibrous adhesions over the pleura. Crepitation was absent in the lower lobe and at the hilus. The cut surface showed small grayish areas of consolidation along the posterior margin of the lower lobe. Frank pus was expressed in places. At the hilus and spreading along the bronchial trunks into the lower lobe were several areas of consolidation, grayish white, firm and rubbery and sometimes sharply defined. Within them were dilated cystic cavities, the largest of which measured 1.5 cm. in diameter. The latter was filled with a yellowish oil. The left lung weighed 282 Gm. Crepitation was slighty reduced. The cut surface showed an area of consolidation in the lower lobe which was similar in appearance to that seen at the hilus of the right lung (fig. 2*A*). There were several enlarged bronchial lymph nodes, deeply discolored with carbon but showing several small areas of apparent fibrosis.

CASE 4.—A white man aged 79 years had hematuria and suffered from severe pain in the right side of the abdomen. On three previous admissions, the patient had suprapubic cystotomy for the removal of vesical calculi and transurethral resection of the prostate to control unexplained hematuria. He also had hypertension and attacks of auricular fibrillation. On the present admission, his bladder was irrigated. He continued to complain of severe abdominal pain, which was thought to be due possibly to mesenteric thrombosis. He suddenly became

cyanotic and died twenty-four hours after admission. The patient had suffered from irritation in his nose for several years prior to death and was accustomed to spray ephedrine oil into it with an atomizer from time to time. He would use the oil twice a day or so for a day or two and then not again for several weeks. This continued over a period of about three years prior to his death.

Necropsy.—The major observations were carcinoma of the prostate, bilateral pyelonephritis and mesenteric thrombosis. The right lung weighed 550 Gm. and the left 350 Gm. There were diffuse hypostatic edema and congestion. There were several hard tumor-like masses scattered through the lungs, particularly subpleurally, which were slightly raised over the surface and measured from 3 to 5 cm. in diameter and from about 1 to 2 cm. in height; the pleural covering over them was smooth and shiny, while the intervening pleura was sometimes wrinkled. Each mass was well demarcated from the surrounding parenchyma. The cut surface was well delimited from the surrounding parenchyma and showed a firm rubbery fibrous tissue, dry and grayish, with yellow mottled areas scattered in it. On casual examination the appearance suggested metastatic nodules from the prostatic carcinoma, and the condition was so diagnosed grossly (fig. 2*B*).

CASE 5 (made available through the permission of Drs. E. L. Gardner and R. S. Ylvisaker, Minneapolis).—A man aged 85, who had had an attack of coronary thrombosis five years before and was suffering from hypertension (224 systolic and 84 diastolic) with complete auriculoventricular block and from enlargement of the prostate, was admitted because of acute infection of the lungs. There was impairment of resonance in the right side of the chest, with many medium moist râles, the breath sounds were diminished anteriorly, and a small area of bronchial breathing was discovered low down posteriorly. The heart was moderately enlarged in all directions. The patient's lips were cyanotic. The roentgenograms of the chest showed an area of consolidation with evidence of atelectasis in the lower lobe of the right lung.

The signs of acute infection in the right lung subsided after the first week, leaving, however, an area of impaired resonance and distant breath sounds. Then symptoms of myocardial insufficiency developed with attacks of dyspnea and cyanosis, necessitating the use of the oxygen tent.

Because of the persistence of the original area of consolidation after all signs of an acute process had cleared up, the continued pain in the chest and bloody sputum, together with evidence of atelectasis on the affected side, the presence of carcinoma of a bronchogenic type was thought probable. However, metastatic carcinoma and some form of chronic pneumonia could not be ruled out (fig. 2*C*).

Nineteen high voltage roentgen treatments were given without any appreciable improvement.

The patient became very weak; a slight fever developed with a few moist râles in the right lung and with complete retention of urine in the bladder, and the patient died suddenly.

Subsequently, it was revealed that for many years he had used oil sprays in his nose and throat daily.

Necropsy.—The major findings included coronary sclerosis and prostatic hypertrophy. The right lung weighed 500 Gm. It showed an area of consolidation in the middle lobe and in the interlobar regions of both upper and lower lobes. The cut surface of the consolidated portion had a waxy, greasy appearance, and from it no fluid could be expressed. The left lung, weighing 750 Gm., crepitated throughout except a small area about 3 cm. in diameter in the base. The

appearance here was similar to that in the opposite lung. The appearance suggested extensive unresolved pneumonia (fig. 2*D*).

Microscopically, the pulmonary lesions found in cases 2, 3, 4 and 5 were essentially identical. They showed chronic fibrosing granulomatous inflammation in various stages of development. They included (*a*) widely spreading proliferation of connective tissue cells, which obliterated the usual alveolar network; (*b*) diffuse infiltration by plasma cells and lymphocytes in varying numbers and by macrophages, usually loaded with emulsified oil; (*c*) capillary engorgement and extravasation in the more cellular areas; (*d*) presence of foreign body giant cells and multinucleated cells, most conspicuously as crescents along the inner lining of rounded alveolar spaces (figs. 3, 4*A* and 5*B*). Conspicuously scattered about in the regions of the hilus (case 3) were tubercle-like formations, which represented the scantily cellular pink-staining masses of "organized" oil and the more cellular connective tissue whorls formed around the blood vessels (figs. 4*B* and 5*A*). In case 5 there were shown many areas of extensive fibrosis, in which the cellular elements were reduced to the minimum and which were sharply separated from the adjacent parenchyma. Sometimes there was a wide stretch of connective tissue growth, which often formed many fenestra engulfing the globules of oil (fig. 6*A* and *B*).

COMMENT

No definite information as to the manner of the administration of oil was available in cases 1 and 2. A history of dysphagia was given in case 2, and this difficulty may have been a contributing factor. In the remaining 3 cases the patients gave the history of instillation or spraying of mineral oil preparations into the nose for difficulties in the upper respiratory tract. These 3 patients were also the victims of cardiac disease.

In case 1 the lesion, which was mistakenly diagnosed grossly as lobar pneumonia and later diagnosed as acute fatal pulmonary fat embolism, represented diffuse interstitial pneumonitis, considered to be an early stage of lipoid pneumonia of the adult type.

The remaining 4 cases exemplified a more chronic and tumor-like process, typifying lipoid pneumonia of the adult type. The pulmonary lesions in cases 2, 3 and 4 were accidentally found at necropsy. Their identity in cases 2 and 3 was suspected grossly and readily confirmed microscopically, while the multiple tumor-like nodules throughout the lungs in case 4 were diagnosed as metastases of carcinoma. The massive lesion in case 5, presenting the clinical and roentgenologic signs of bronchogenic cancer, was regarded as unresolved pneumonia at necropsy, the exact nature of which was appreciated only through the histologic examination.

Of practical importance is the clinical and roentgenologic differentiation of pulmonary lesions of the type described from neoplasms.

particularly bronchogenic carcinoma. This is now possible through obtaining an accurate history and observing physical signs. Pathologically, it appears that the gross appearance of the typical pulmonary lesion may be only suggestive, but the histologic picture is always unmistakably characteristic and diagnostic.

SUMMARY

Lipoid pneumonia of the adult type is a distinct clinicopathologic entity. Liquid petrolatum is the chief etiologic agent. The condition occurs predominantly among older persons. There is usually a history of chronic infection of the upper respiratory tract. Oil is applied in the upper air passage; most commonly it is sprayed or instilled into these airways; it is as a rule self-administered in large quantities for a long time. The pneumonia develops slowly, extending over a period of years, accompanied invariably by recurrent bronchopulmonary symptoms. The typical pulmonary lesion represents a chronic nonspecific nonsuppurative granulomatous foreign body reaction leading to ultimate tumefaction and fibrosis; in its clinical behavior and roentgenographic appearance it simulates a neoplastic growth in the lung; it has been mistaken for a tumor at necropsy; it is essentially a paraffinoma of the lung.

Like lipoid pneumonia of the infantile type, lipoid pneumonia of the adult type is more common than hitherto generally suspected. It can be diagnosed clinically, and it is to a large measure preventable through intelligent application of the otherwise useful preparations of liquid petrolatum.

Because of the increasing and uncontrolled use of preparations of liquid petrolatum by lay people in the treatment of their respiratory difficulties, a possibility of lipoid pneumonia of the adult type (paraffinoma), which frequently simulates a neoplasm in its clinical behavior, should always be borne in mind in the differential diagnosis of obscure pulmonary conditions.

THE WEIGHT OF NORMAL ADULT HUMAN KIDNEYS AND ITS VARIABILITY

HERBERT WALD, PH.D.
MINNEAPOLIS

Records of the weight of the kidneys and of the variation in this weight are not common in early literature. Vierordt,[1] in his tables of the weight of the kidneys, gives a complete record of the sources of his data, which included all of the available material at that time. Greenwood [2] and Greenwood and Brown [3] were the first to apply modern statistical methods to the study of weights of human organs and to define adequately the disease categories used.

Until recently, all standards of the weights of organs were based on organs from persons who had died of disease; this was due to the absence of adequate data on the weights of organs of physiologically normal persons. In 1933 and 1934 de Leon and his co-workers [4] at the University of the Philippines established statistical standards for the normal weights of the visceral organs of Filipinos by obtaining the viscera in 768 cases of accidental death, in most of which death was immediate and not accompanied or preceded by any known pathologic state.

Boyd,[5] in her studies of the variability of the weights of certain organs, selected cases of accidental death from the necropsy records of the department of pathology of the University of Minnesota for use in arriving at weights of organs that would be typical of physiologically normal persons. She found that the distribution of the weights of the organs which she studied did not follow the normal curve and that the limits of their variation could not be adequately defined by multiples of the standard deviation. She then reintroduced the older percentile method, which, she found, described the limits of variation more satisfactorily.

From the Department of Anatomy of the University of Minnesota Medical School.

1. Vierordt, H.: Anatomische, physiologische und physikalische Daten und Tabellen, Jena, Gustav Fisher, 1906.

2. Greenwood, M.: Biometrica **3**:63, 1904.

3. Greenwood, M., and Brown, J. W.: Biometrica **9**:473, 1913.

4. de Leon, W.; de Jesus, P. I., and Ramos, J. M.: Philippine J. Sc. **54**:495, 1934. de Jesus, P. I.; de Leon, W., and Ramos; J. M.: ibid. **52**:119, 1933. de Leon, W.; Garcia, A., and de Jesus, P. I.: ibid. **52**:111, 1933.

5. Boyd, E.: Am. J. Dis. Child. **43**:1162, 1932; **51**:313, 1936; Arch. Path. **16**:350, 1933; Anat. Rec. **62**:1, 1935.

In this study the weights of organs used in determining the normal weight of the kidneys were selected by reference to the necropsy records of the department of pathology of the University of Minnesota for the years 1920 to 1935, inclusive, and met the specifications set down by Boyd [5] in her report on the normal variation in the weights of the liver and spleen; that is, the normal category included only the organs from cases in which the cause of death was an accident, in which death occurred within twenty-four hours after the accident, in which there was no history of recent illness or any distinct pathologic abnormality at necropsy and in which there was no gross hemorrhage. All cases in which there was a diagnosis of hemothorax, hemoperitoneum, hemopericardium or rupture of the liver, spleen, or a large blood vessel were included in the category of cases of gross hemorrhage. Altogether, 414 "normal" weights were collected, 307 for males and 107 for females,

TABLE 1.—*Statistical Parameters of the Normal Weight (in Grams) of Both Kidneys According to Age and Sex*

	Male				Female			
Age, Years	Number of Weights	Mean Weight ± S. E.*	Standard Deviation	Coefficient of Variation, per Cent	Number of Weights	Mean Weight ± S. E.	Standard Deviation	Coefficient of Variation, per Cent
20 to 29	55	313 ± 7.96	59.0	18.9	29	257 ± 10.11	54.5	20.2
30 to 39	72	323 ± 6.72	57.0	17.6	21	250 ± 10.39	47.6	19.1
40 to 49	81	316 ± 6.04	54.4	17.2	21	258 ± 11.52	52.8	20.5
50 to 59	46	294 ± 7.66	52.0	17.6	13	254 ± 18.46	66.5	26.2
60 to 69	36	293 ± 10.89	65.3	22.2	17	218 ± 9.79	40.4	18.5
70 to 79	17	253 ± 7.78	32.1	12.7	5	236 ± 22.24	49.7	21.1

* Standard error of the mean.

to be used in calculating the statistical constants for the weight of both kidneys combined, the relationship of their weight to that of each of the other organs and the construction of normal standards of variation in the weight of the kidneys.

The various statistical constants for the weights of this carefully selected group of normal kidneys are given in table 1. The mean weight for each decade from 20 to 80 years indicates that the weight is stationary until about the sixth decade, when it begins to decrease. This age trend is in accord with the findings of Bean and Baker,[6] Castaldi and Vannucci [7] and de Jesus and his co-workers.[4]

In all but the eighth decade, for which the number of weights was only 5 for females, the mean weights of the kidneys for males were from 40 to 75 Gm. larger than those for females. These differences are from two to five times their standard errors, hence chance would not

6. Bean, R. B., and Baker, W.: Am. J. Phys. Anthropol. **2**:265, 1919.
7. Castaldi, L., and Vannucci. D.: Scritti biol.. 1927, p. 3.

account for them more often than from one to twenty times in a thousand. This is in agreement with the usual sex differences in size.

These mean weights from cases of traumatic death tend to be less than those reported since 1900 for Caucasians dying of disease. This finding supports the common impressions of pathologists and the findings of experimental biologists (Jackson,[8] 1929) that many diseases cause slight enlargement of the kidneys. Only one contemporary report based on kidneys in persons dying of disease (Castaldi and Vannucci [7]) gave mean weights of the kidneys close to those of the normal group presented here. This discrepancy may be accounted for by the smaller normal organs of the smaller peoples being raised in weight by disease to the level of the normal kidneys of the larger peoples.

Neither the absolute nor the relative variability of the weight of the kidneys as shown by the standard deviation and the coefficients of variation in table 1 changes markedly from decade to decade until the seventh and eighth decades in either sex. The fluctuation from 22 to 12 per cent in the coefficients of variation for males in the last two decades may be accounted for by errors in the sampling. The coefficient of variation of approximately 17 per cent for males in the third to sixth decades of life is slightly but not significantly less than the average coefficient of 21.05 per cent reported by Greenwood and Brown [3] for a selected hospital population. However, the tendency toward smaller variation in normal organs is in line with the observation of Greenwood and Brown in that the organs of their selected group were significantly less variable than those of the general hospital population.

The coefficients of variation for males are slightly but not significantly lower than those for females. Thus, for males, two thirds of all the weights of the kidneys fall within a range of 17 per cent above and below the mean, while the range of weights for females is slightly but not significantly greater.

For males the coefficients of correlation between the weight of both kidneys and the weights of other organs are: liver, 0.60; heart, 0.32, and spleen, 0.23. The coefficient of correlation with body length is 0.22. When age is held constant, the coefficients become 0.57, 0.38, 0.17 and 0.22, respectively, thus indicating the slight influence of age on the interrelationship of kidney weight and the weight of each of the other organs and body length. These values agree rather closely with the coefficients of correlation between the same measurements given by Greenwood and Brown.[3] About half of the organs used by these authors were from persons whose deaths were due to diseases which, according to the pathologic diagnoses, did not directly affect the organs, and half from persons

8. Jackson, C. M.: The Effects of Inanition and Malnutrition upon Growth and Structure, Philadelphia, P. Blakiston's Son & Co., 1925; Arch. Path. **7**:1042, 1929; **8**:81 and 273, 1929.

who came to accidental death. Therefore, the fundamental relationship between organs does not seem to be affected by disease processes that do not affect the organs directly.

For females, the coefficients of correlation between the weight of both kidneys and the weights of other organs are: liver, 0.46; heart, 0.42, and spleen, 0.39. The coefficient of correlation with body length is 0.26. When age is held constant, the coefficients become 0.45, 0.56, 0.37 and 0.30, respectively. These coefficients are not significantly different from those between the similar measurements for males.

In order to obtain for each sex a standard chart of age trend and normal variation that would cover the adult period, a graph was constructed from the means and ± 1 and 2 standard deviations (σ) from the mean for each decade. By definition of the standard deviation, the zone

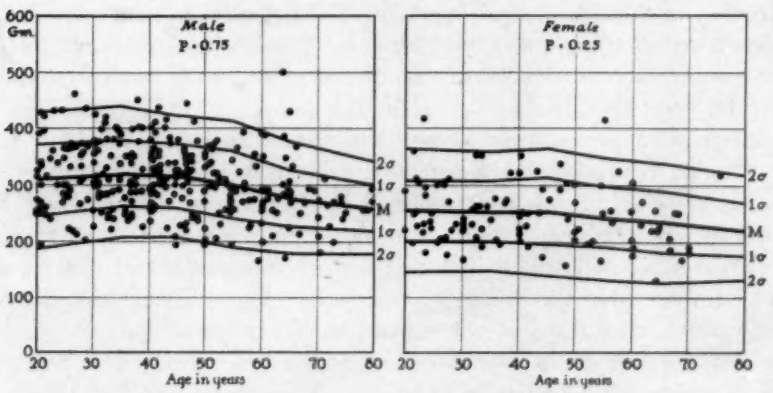

Chart 1.—Standards of normal variation in the weight of both kidneys for both sexes, based on the means (M) and standard deviations (σ) for each decade given in table 1. The original weights are indicated by dots.

within the ± 1σ lines would be expected to include 68 per cent of the weights, and the zone within the ± 2σ lines, 95 per cent of the weights. These standards for males and females, respectively, with the original values plotted on them, are given in chart 1. According to the probability integrals (P) on the graph as calculated by Chi-square (Boyd,[5] 1933, 1935), the likelihood that the differences between the expected and the observed number of cases in each sigma zone arose by chance is seventy-five times in a hundred for the male standard and twenty-five times in a hundred for the female, indicating that the difference between the observed and the calculated value can be accounted for by chance alone.

This type of standard, however, has proved unsatisfactory in defining the limits of variation in the weight of the thymus (Boyd,[5] 1932), the weights of the liver and spleen (Boyd,[5] 1933) and the weight of the

heart (Textor).[9] Boyd pointed out that the use of the standard deviation to construct standards of normal variability failed for the weights of the liver and spleen because the weights do not closely approximate a normal distribution. She found that although the degree of skewness commonly observed for the weights of most organs was sufficient to invalidate the use of multiples of the standard deviation to define the probable limits of normal variation, it was not sufficient to invalidate the use of the standard deviation in comparing the variability of two samples or in describing the central zone of variation. She found also that the probable limits, as well as the central zone of variation, could be adequately described by the older percentile method.

In order to have comparable standards of variation in weight for all organs, Boyd's [5] (1935) method of constructing a percentile standard

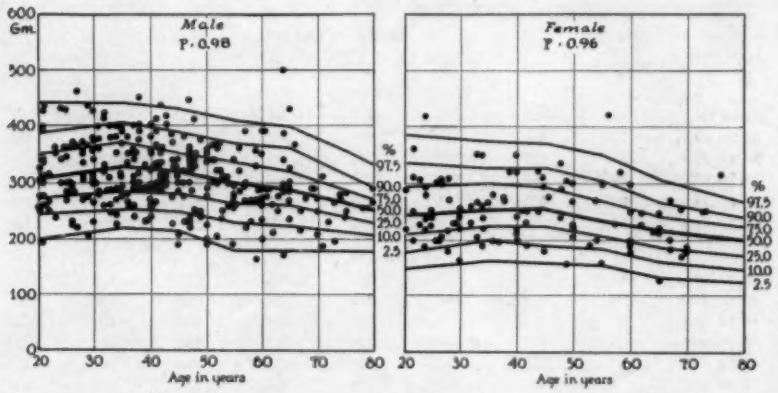

Chart 2.—Standards of normal variation in the weight of both kidneys for both sexes, based on the percentile standards for each decade given in table 2. The original weights are indicated by dots.

was used. In this standard (chart 2 and table 2) the zone between the 25 and 75 percentile lines, expected to contain 50 per cent of the weights, is comparable to the zone demarcated by ± 1 probable error (P. E.) around the mean of a normal distribution. Likewise, the zone between the 10 and 90 percentile lines, expected to contain the middle 80 per cent, is roughly comparable to ± 2 P. E., and that between the 2.5 and 97.5 percentile lines, to ± 3 P. E.

When the weights of the kidneys were plotted on this standard, the observed number in each zone corresponded closely with the expected number. When the Chi-square test was applied, the probability integrals (P) were 0.98 for the male and 0.96 for the female. Hence, the percentile standards may be assumed to be adequate descriptions of the

9. Textor, J.: Unpublished work from this department.

variation in weight of both kidneys of the adult human male and the adult human female. In fact, since these probability integrals show closer approximation of the observed values to the standard, the percentile standard for each sex may be assumed to be a better description of the variation in the weight of both kidneys in this series.

According to this standard, the median weight of both kidneys in the third decade of life is for males about 308 Gm. The weight increases slightly through the third and fourth decades until it reaches approximately 320 Gm. and then definitely decreases to approximately 260 Gm. in the eighth decade, a loss of 18 per cent. For females, the mean weight of both kidneys is approximately 60 Gm. less than for males and follows the same general trend with age as for males. As would

TABLE 2.—*Smoothed Percentiles of Weight for the Normal Kidneys*

Age Interval, Years	Number of Weights	Percentiles of Weight in Grams						
		97.5	90	75	50	25	10	2.5
				Males				
20 to 29	55	442	393	353	310	275	240	203
30 to 39	72	440	405	370	322	284	250	220
40 to 49	81	430	385	350	319	284	245	213
50 to 59	46	407	365	334	295	262	225	180
60 to 69	36	403	358	320	283	260	224	180
70 to 79	17	353	312	285	260	237	210	184
				Females				
20 to 29	29	380	332	297	248	215	176	157
30 to 39	21	372	330	300	251	225	198	165
40 to 49	21	370	332	295	254	225	191	160
50 to 59	13	350	304	267	233	203	184	158
60 to 69	17	307	265	240	218	188	164	135
70 to 79	5	280	250	228	205	178	157	130

be expected from the close approach of the weights of the kidneys to a normal distribution, the central trend, as measured by the median, does not differ appreciably from the mean.

The variability of the weight of the kidneys, as illustrated by the various zones on the standard, shows that on the average the middle 50 per cent of weights covers a range of 70 Gm. in males and 65 Gm. in females, the middle 80 per cent a range of 140 Gm. in males and 125 Gm. in females, and the middle 95 per cent a range of 220 Gm. in males and 190 Gm. in females. In relative terms, the 75 percentile line averages 13 per cent above the median line for males and 16 per cent for females, while the 25 percentile line averages 10 per cent below the median for males and 12 per cent below for females. The 97.5 percentile line averages 40 and 46 per cent above the median for males and females, respectively, while the 2.5 percentile line averages 35 and 36 per cent below. These findings indicate a slight but definite skewness in the distribution of the weights of the kidneys in both sexes.

When the weights of kidneys from persons whose accidental deaths were associated with gross hemorrhage were plotted against the normal standard (chart 3), an undue proportion of weights fell into the lower percentile zones. The probability that this disproportion arose by chance sampling is, according to the Chi-square test, less than 1 in 1,000 in either males or females.

This finding, that the weight of the kidneys is materially lowered with gross hemorrhage, is in accordance with the findings of Boyd [5] (1933) for the liver and spleen. In males, the average percentage of the weight loss of the kidneys with gross hemorrhage was 9.1, as compared with 10.9 for the liver and 15.5 for the spleen. No difference in the effect of gross hemorrhage on the weights of these organs corresponding with sex difference was noted.

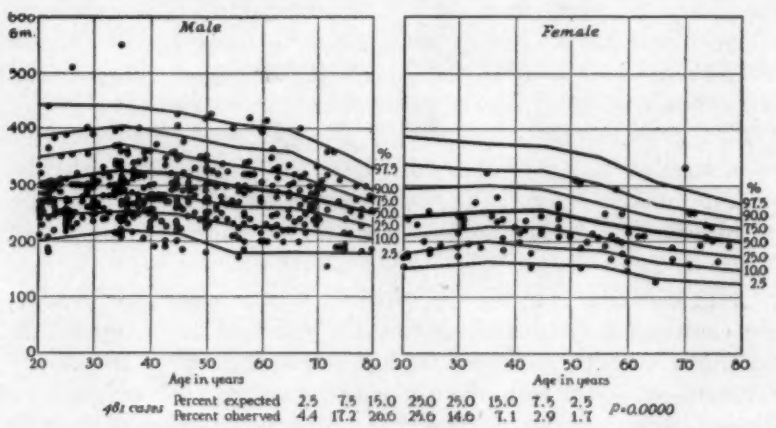

Chart 3.—Graphs showing the weights of both kidneys in normal males and females dying of trauma with gross hemorrhage, plotted on the percentile standards of normal variability of the weight of both kidneys; p is the probability integral.

COMMENT

The chief value of the percentile charts presented here as standards of variation of the normal weight of the kidneys over and above means and their standard errors for age periods is that they make possible the comparison of small series of kidney weights from both sexes throughout the entire adult age range without any subdivision of data. As regards many pathologic conditions, less than 50 cases are available for study. If this small group is divided into two sex groups and then into two or three age groups, the various subgroups are numerically too small for reliable statistical comparison of the means. Moreover, the weights of the kidneys for a given disease can be plotted on the standard as the data are gradually collected, and an impression of age

and sex trends may be gained before sufficient data have been collected to justify the tedious calculation of the means and standard deviation.

While the 2.5 and 97.5 percentile lines may be considered reasonable approximations of the lower and upper limits of normal variation, two or three weights in every hundred in normal subjects, as can be judged by ordinary pathologic diagnosis, will fall above the 97.5 percentile line, and two or three, below the 2.5 percentile line.

The percentile standard for males is undoubtedly more reliable than that for females, since the former was based on almost three times as many cases as was the latter.

SUMMARY

The means, standard deviations and coefficients of variation in the weight of both kidneys for both sexes by decades of the age period from 20 to 80 years have been presented. These parameters were calculated from the weights of kidneys from persons dying of accidents within twenty-four hours after injury, without gross hemorrhage, or disease demonstrable at necropsy and without a history of recent illness.

The interrelationship between the mean weight of the kidneys and that of each of various organs was measured by calculating directly the coefficient of correlation. The results obtained for normal organs are in fair agreement with similar reports in the literature for organs from persons dying of disease.

Graphic standards of normal variability in the weight of the kidneys were constructed from multiples of the standard deviation and from percentiles, for both sexes, for the age period from 20 to 80 years.

When compared with the percentile standard, the weight of the kidneys in persons dying of trauma accompanied by massive hemorrhage was materially reduced.

THE RÔLE OF ALLERGY IN THE PATHOGENESIS OF PROGRESSIVE THROMBOSIS

ESPECIALLY IN REGARD TO CHANGES IN THE ENDOTHELIAL LINING OF LARGE PERIPHERAL VEINS

JOSEPH TANNENBERG, M.D.
ALBANY, N. Y.

An interplay of slow blood flow, pathologic changes in the venous wall and changes in the composition of the blood fluid is usually considered the leading factor in the pathogenesis of progressive thrombosis in the large veins. In earlier communications based on experiments, especially on microscopic observations in the living animal, and on experience of human pathology we (Tannenberg and Fischer-Wasels [1]) emphasized particularly the rôle of local blood changes, produced just in the organ or the extremity where thrombosis was developing. Furthermore, we considered it helpful in further studies to distinguish the following three types of thrombosis in each of which the pathogenesis might be different as their significance is for the patient and for the physician: (1) local thrombosis in the presence of wounds, (2) thrombosis due to infection and (3) progressive "distant" thrombosis in large veins, independent of any local disturbances.

Dietrich [2] and his collaborators emphasized particularly the rôle of the venous endothelium in the pathogenesis of progressive thrombosis. They emphasized this not in the sense that thrombosis may be due to the primary phlebitis of the old French authors (Cornil, Widal, Vaquez [3]) or to the mechanical unevenness of the intima (Ribbert [4]) but that it may result from an allergic reaction of the endothelium to certain substances carried in the blood. By often repeated injections of foreign protein or of killed germs in experiments on animals they tried to produce such high sensitivity of the common endothelium of the large

From the Research Department of the Bender Hygienic Laboratory.

1. Tannenberg, J.: Ztschr. f. Geburtsh. u. Gynäk. **73**:349, 1926. Tannenberg, J., and Fischer-Wasels, B.: Die Thrombose, in Bethe, A., and others: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1927, vol. 7, p. 1726; Deutsche med. Wchnschr. **55**:524 and 574, 1929.

2. Dietrich, A.: Thrombose, ihre Grundlagen und ihre Bedeutung, Berlin, Julius Springer, 1932; Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch. **7**:48, 1934.

3. Vaquez, H.: De la thrombose cachetique, Paris, G. Steinheil, 1890.

4. Ribbert, H.: Deutsche med. Wchnschr. **38**:1577 and 2270, 1912.

veins that it would react to the specific antigen of the preparatory treatment as well as to any foreign protein or germs with which it came into contact (Dietrich and Siegmund [5]). Dietrich and Schröder [6] stated that they had elicited in a surprisingly short time marked endothelial proliferations in large veins of allergic animals. They regarded them as the morphologic equivalent of the high sensitivity of these animals. These results form the morphologic basis of their theory that such endothelial reactions are the most important factor in the pathogenesis of progressive thrombosis. Their view was accepted by some authors, as Henschen,[7] Zschau,[8] von Seemen,[9] Serdjukoff and Jegoroff [10] and Beischer [11] and contested by others, as Ewald,[12] Apitz,[13] Ohm [14] and Aschoff.[15] My associates and I made experiments as follows in order to base our opinion on our own studies.

METHOD AND TECHNIC

Using rabbits weighing about 2,000 Gm. each, we prepared three groups with three different antigens, respectively, giving nine intravenous injections alternately into the veins of both ears of each rabbit in the course of three weeks. The first group was treated with streptococci of a strain isolated from a patient with arteritis nodosa, the second with pneumococci, type I, and the third with sheep serum. The reinjection of the same antigen was always given into the vein of the right ear between the seventh and eighteenth day following the last preparatory treatment. Just before the reinjection, the right jugular and femoral veins were exposed and narrowed by ligatures of silk or cotton threads or strips of fascia split off in situ. The operations were performed under sterile conditions and ether anesthesia. Especial care was taken to avoid hemorrhages and any unintentional injury to the vessels. The rabbits were killed twenty-four hours later by administering chloroform or by exsanguination. A thorough gross examination of the entire animal was made. The ligated veins and the corresponding ones from the other side, as well as various other veins, were preserved in solution of formaldehyde U. S. P. (1:10) and later studied in serial sections

5. Siegmund, H.: München. med. Wchnschr. **72**:639, 1925; Verhandl. d. deutsch. path. Gesellsch. **19**:114, 1923; **20**:260, 1925.

6. Dietrich, A., and Schröder, K.: Virchows Arch. f. path. Anat. **274**:424, 1929.

7. Henschen, F.: Acta med. Scandinav. **65**:539, 1927.

8. Zschau, H.: Deutsche Ztschr. f. Chir. **230**:13, 1931.

9. von Seemen, H.: Arch. f. klin. Chir. **162**:222, 1930; Deutsche Ztschr. f. Chir. **223**:1, 1930.

10. Serdjukoff, M. G., and Jegoroff, B. A.: Monatschr. f. Geburtsh. u. Gynäk. **99**:56, 1935.

11. Beischer, K.: Beitr. z. path. Anat. u. z. allg. Path. **94**:501, 1935.

12. Ewald, W.: Beitr. z. path. Anat. u. z. allg. Path. **83**:681, 1931.

13. Apitz, K.: Virchows Arch. f. path. Anat. **289**:46, 1933; **293**:1, 1934; Ztschr. f. d. ges. exper. Med. **94**:222, 1934.

14. Ohm, W.: Beitr. z. path. Anat. u. z. allg. Path. **96**:491, 1936.

15. Aschoff, L.: Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch. **7**:11, 1934.

after having been embedded in paraffin, paraffin-pyroxylin (celloidin or pyroxylin celloidin). The usual staining methods, including Heidenhain's azan and Mallory's and Weigert's fibrin-staining methods, were applied. For controls we used rabbits which were given only one injection of bacteria following the narrowing of the veins, or sensitized rabbits which were given reinjections of an antigen different from that of the sensitization. The bacteria were prepared as follows: ten cubic centimeters of an eighteen hour broth culture was centrifugated. The supernatant fluid was discarded. Then 1 cc. of 0.2 per cent solution of formaldehyde U. S. P. was added. These bacteria were injected in a dosage increasing from 0.5 to 1.5 cc., for preparation. For reinjection, from 3 to 5 cc. was given, or 2 cc. of a broth culture of living bacilli (twenty-four hour culture). The serum dosages were increased from 2 to 3 cc. for preparation, and from 10 to 12 cc. was used for reinjection.

The number of rabbits in the various series and the kind of treatment given them are shown in the accompanying table.

RESULTS

The gross examination of the killed rabbits revealed in only one of the pneumococcic series a kind of progressive thrombosis. In all others there were merely small localized thrombi from 0.1 to 0.5 cm. long in the venous segments distal to the ligatures. The thrombi of the immunized rabbits were on the average not larger than those of the controls. Proximal to the ligature there was in no case grossly a thrombus recognizable. In the single instance of a kind of progressive thrombosis of the jugular vein, the segment proximal to the ligature also was free, collapsed and empty. But distal to the narrowed site, in the middle of the jugular trunk, the vein with all its branches was distended to its maximum extent and thrombosed. From there the thrombus extended to all branches proceeding to the jaw as well as to the right ear. Veins smaller than the main vein of the ear, however, were not involved. The gross examination revealed in this instance very striking changes in both kidneys, which were considered responsible for the exceptionally large extent of the thrombosis. Their whole cortical surface presented numerous irregularly distributed shallow scars from 1 to 2.5 mm. in diameter and irregular in size and shape. At the cut surface they were contiguous with the parenchyma and converged as fine or thick streaks toward the renal pelvis. Both kidneys were markedly shrunken as a result of this process. Histologically there was in both kidneys a widespread chronic inflammatory process, which was still progressive and had already destroyed a considerable portion of the renal tissue.

In all cases, the narrowed veins and the controls were carefully studied histologically, mostly in sections parallel to the venous axis, but partly in cross-sections.

In the region of the operation, a moderate leukocytic infiltration of the connective tissue, involving the adventitia of the vein, was present, but no large amount of pus and no abscesses were found. The ligated area of the vein revealed marked diffuse infiltration of the adventitia. In the thinner femoral vein, often the entire wall was infiltrated, while in the jugular vein the infiltration usually was confined to the adventitia and the outer part of the media. The endothelium was often partially covered by leukocytes, and here and there a few leukocytes had invaded the intima and were observed directly beneath the endothelial lining. Sometimes, microscopically, slight hemorrhages into the adventitia or the surrounding connective tissue were present. In such an area the leuko-

cytic infiltration was usually somewhat more marked. Occasionally a slight hemorrhage was observed in the inner part of the wall. In such a case a small thrombus was present at the inner surface but was strictly circumscribed and clearly distinguishable by its structure from the other contents of the vein; also, no progressive thrombosis was present. The completely ligated veins exhibited greater injury to the wall beneath the thread and a more marked inflammatory

Rabbits	Sensitization		Ear Vein	Reinjections		Narrowed Veins	Additional Treatment	Time of Death	
	Antigen	Injections		Material	Day Following Last Sensitizing Injection			Following Reinjection	Following Last Sensitizing Injection
3	Killed streptococci	9 intravenously	Right	Killed streptococci	13th	Right jugular and femoral veins		24 hr.	14 days
1	Killed streptococci	9 intravenously	Right	Living streptococci	13th	Right jugular and femoral veins		24 hr.	14 days
1	Killed streptococci	9 intravenously	Right	Living streptococci	13th	Right jugular and femoral veins		9 days	22 days
1	Killed streptococci	9 intravenously	Right	Killed streptococci	13th	Left jugular and femoral veins		24 hr.	14 days
3	Killed pneumococci	9 intravenously	Right	Killed pneumococci	7th	Right jugular and femoral veins		24 hr.	8 days
2	Killed pneumococci	9 intravenously	Right	Living pneumococci	18th	Right jugular and femoral veins		24 hr.	19 days
1	Killed pneumococci	9 intravenously	Both	Killed pneumococci + sheep serum 10 cc.	11th and 12th	Jugular and femoral veins on both sides	Sheep serum	48 hr.	13 days
6	Sheep serum	9 intravenously	Right	Sheep serum	11th to 19th	Right jugular and femoral veins		24 hr.	12 to 20 days
1	Erythrocytes of sheep	6	Right	Sheep serum	90th	Right jugular and femoral veins		7 hr.	90 days
5			Right	Living pneumococci		Right jugular and femoral veins		24 hr.	

reaction than the merely narrowed veins. In the former, there was a distinct but strictly localized necrosis, not larger than a section of a microscopic field. The wall showed here a uniformly homogeneous, hyalinized appearance, and no nuclei were present. At the border of this area a number of leukocytes sometimes formed a real zone of demarcation. The merely narrowed veins did not exhibit any necrosis under the ligature. Here, the inflammatory reaction was only somewhat more marked than elsewhere in the vicinity.

The endothelial lining in the neighborhood of the ligature presented various changes. As a whole it seemed to be wider and more darkly stained than normal. The individual cells had lost the uniform appearance which they normally

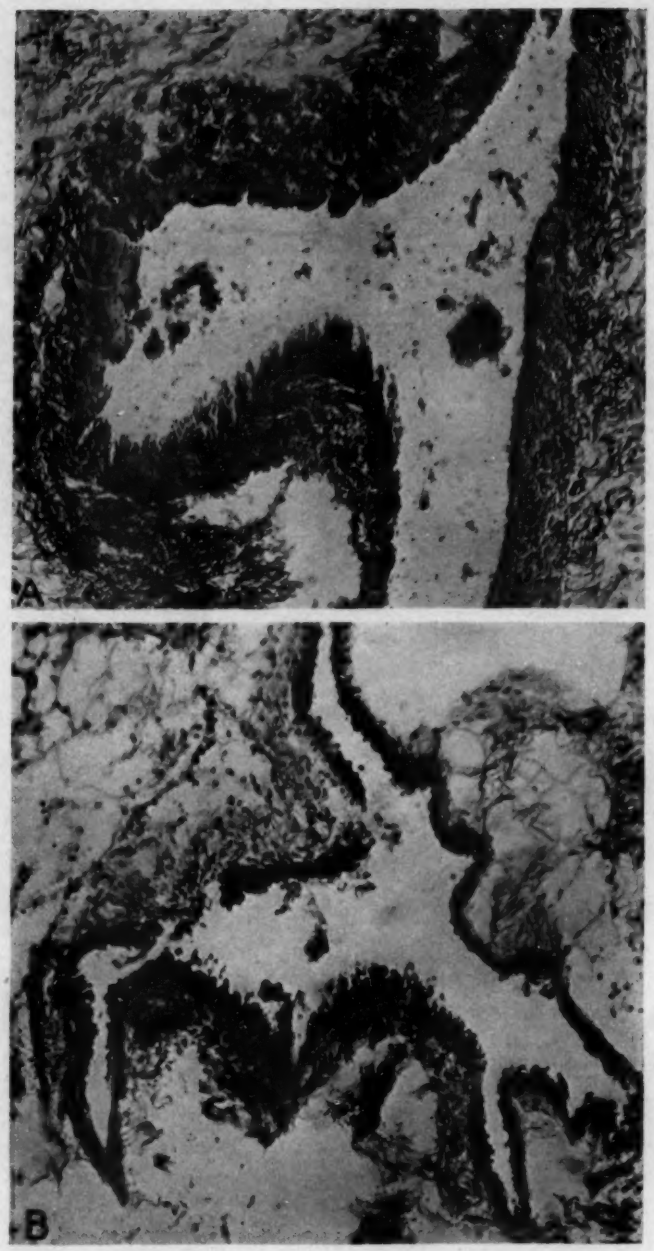

Fig. 1.—Degenerative (pseudoproliferative) changes of the venous endothelium that did not cause thrombosis: *A*, section of a venous area from a rabbit sensitized with and given a reinjection of streptococci. The area shown was in the right jugular vein, proximal to the site of ligation, taken twenty-four hours after the reinjection of the antigen. *B*, an area of a vein of a rabbit that was sensitized with washed erythrocytes of sheep, and given, three months later, a reinjection of sheep serum. The area was in the femoral vein, proximal to the site of ligation, taken seven hours after the injection of serum. It shows that the pseudoproliferation of the endothelium was produced by local folding followed by deposition of blood leukocytes.

present. Frequently they were not as low and flat as usual with corresponding nuclei, but were more or less enlarged or swollen, cubic, more round or even irregular in shape. Their nuclei also were irregularly formed, enlarged, darker-stained and here and there contracted and pyknotic. Occasionally, single cells were loosened or pushed away and the underlying tissue denuded for short distances. The wider and more distinct appearance of the endothelial lining was,

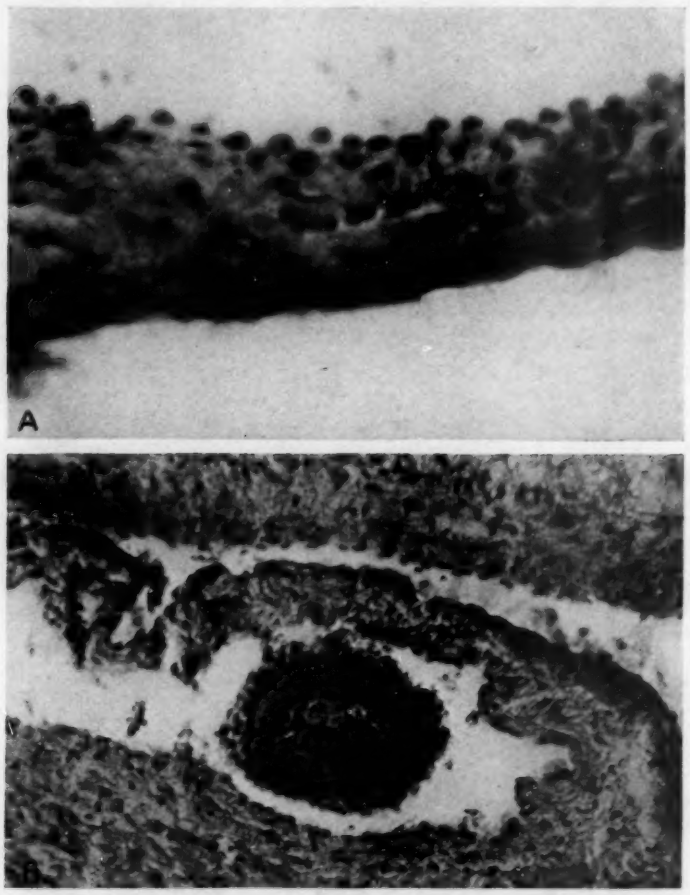

Fig. 2.—*A*, venous area in the right femoral vein of a sensitized rabbit given a reinjection of sheep serum. Note the swelling and loosening of the endothelial cells twenty-four hours after the reinjection. *B*, fibrin-platelet clump free in the angle of a valve of the right jugular vein distal to the site of ligation in a rabbit that was sensitized with killed pneumococci and given a reinjection of living pneumococci.

furthermore, caused by the presence of more or less numerous round cells deposited from the blood stream. These cells were firmly adherent to the endothelial lining, and they also covered the wall where it was denuded of endothelium.

Usually they were found in a single irregular row, but here and there little clumps of two or three cells were adherent to the endothelium. These cells were mostly polymorphonuclear leukocytes, but lymphocytes and monocytes were also present.

The alterations of the endothelium were especially distinct and striking in the relatively empty segment of the vein proximal to the ligature, where the wall was folded by it.

Because of the subnormal blood content in the latter area, there was marked contraction of the muscles and elastic fibers in the venous wall. Both these factors together produced an unusually great folding of the endothelial lining. Therefore, in a section through such an area, especially when it was somewhat tangential, the endothelium sometimes resembled papillomatous structures. In these folds, relatively many leukocytes were adherent to the endothelium. Because of the quiet blood movement here, they settled very often in one, two or three irregular rows or in little clumps.

At first glance, such an area offered a certain resemblance to rapidly proliferating endothelial cells. But a thorough and accurate examination, especially in serial sections, showed that there was no real proliferation of the endothelial cells. It could be clearly observed that the endothelial lining consisted of only one layer, which was folded. These folds filled with leukocytes in irregular rows produced the papilloma-like appearance.

It may be emphasized here that the appearance of the endothelium depended very much on the width of the vessel and the stage of local contraction. This stage of contraction did not depend alone on the degree to which the vessel was filled with blood. It was often strictly determined by local conditions, as microscopic examination revealed (Galloway [16]). In the same microscopic field, sometimes not only contiguous portions of the venous wall revealed different stages of contraction and therefore different shapes of the endothelial cells, but the same observation could be made in longitudinal sections on opposite sides of the same segment of the vein. This is illustrated in figure 1 *A* and *B*. It was not possible to decide here, merely from the sections, whether these local differences were present also in the living vein or were results of irregular contractions following death or even of the influence of the solution of formaldehyde used for fixation.

In the well filled segment of the vein distal to the ligature, the endothelium seemed to be considerably less changed than in the empty, contracted proximal segment. Only in the immediate vicinity of the ligature the aforementioned changes were present. For the rest, the endothelial cells were flat, smooth and apparently unchanged.

It was surprising that usually at that side of the ligature where histologically the endothelial changes were especially marked and striking, namely, proximal to the ligature, no trace of a thrombus was present, but on the other side at least a local thrombus was found. This cannot be explained by the objection that no blood was allowed to enter the segment proximal to the ligature. By the way of anastomoses, which were present in the jugular as well as in the femoral vein, some blood entered this segment, and thereby the first prerequisite for the formation of a thrombus was fulfilled.

We paid special attention to the endothelial lining of the veins in areas of valves because such areas are so often favorable to the formation of thrombi. But there was no morphologic evidence of specific sensitivity.

16. Galloway, R. J. M.: Am. J. Path. **12**:333, 1936.

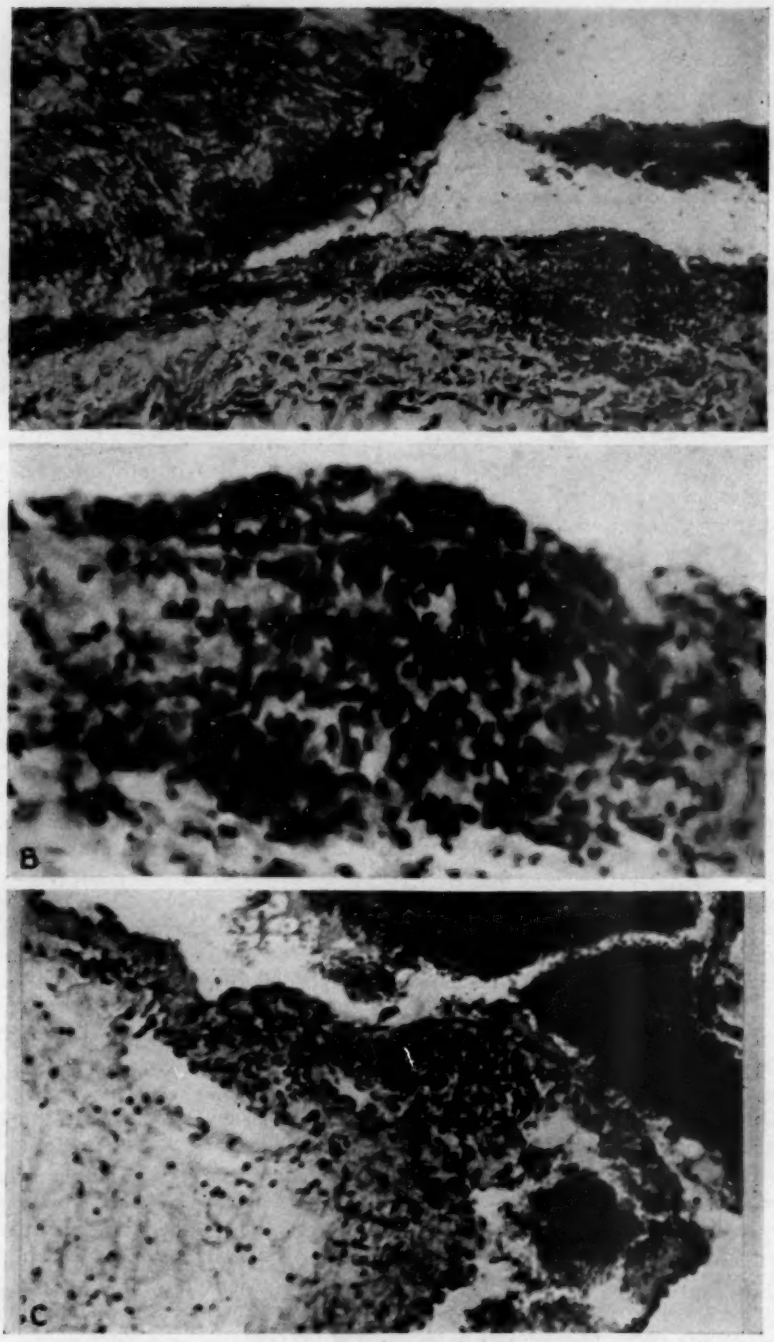

Fig. 3.—Acutely and chronically inflamed foci in a venous wall that did not cause even a local thrombus. *A*, focus of round cell infiltration of the wall of the left jugular vein of a rabbit sensitized with killed pneumococci and given a reinjection of living pneumococci in the right ear vein. *B*, a part of *A* as seen under high power magnification. *C*, section of right jugular vein distal to the site of ligation from a rabbit sensitized with and given a reinjection of sheep serum. Note that a focus in the venous wall, directly at the basis of a valve, is acutely infiltrated by polymorphonuclear leukocytes. The endothelium is not involved.

Another series of six rabbits which were given repeated injections of sheep serum containing carmine also failed to show any sign of specific activity of the venous endothelium in the areas proximal and distal to the ligatures.

As already mentioned, in the femoral as well as in the jugular veins, small thrombi were found in the distended and congested segments distal to the ligatures. Structurally they usually were coagulation thrombi; i. e., they were composed of all the morphologic elements of the blood in almost normal distribution, especially of densely packed erythrocytes. Sometimes they showed distinctly formed whorl structures, which easily allowed them to be distinguished from a simple clot. But also their dense structure itself differentiated them from the unclotted blood with which they were surrounded. These thrombi were always relatively small and strictly confined to the immediate vicinity of the ligatures. They cannot be compared with progressive thrombosis in man.

In the femoral vein, occasionally, a very small platelet thrombus was found directly adherent to the site of the ligature. It was chiefly composed of coagulated layers of platelets, including more or less numerous leukocytes, which were partly broken to pieces. By the interspersing of these leukocytes or of the débris of their nuclei, the whorl structure of the small thrombus was emphasized. Such thrombi, too, were small and in no case progressive. In a few instances such a thrombus was contiguous through the site of the ligation to the venous segment proximal to it. But there it also remained strictly localized. On the other hand, in several instances, in branches of the ligated jugular vein, there were found in the angles formed by the valves small whorled thrombi, apparently produced in these angles by the slowly whirling blood but having no connection with the venous wall. These small thrombi were generally made up of platelets intermingled with more or less broken leukocytes. In the area where they were found, there was no morphologically recognizable alteration of the endothelial lining of the valves or of the venous wall. Neither was there any inflammatory infiltration of the other parts of the wall. The animals which received reinjections of living bacilli did not show any reaction different from that of the rest of their series.

In the wall of the jugular vein, in a few rabbits of the pneumococcic and serum series, there were present several circumscribed small foci of chronic inflammatory infiltration. The whole width of the wall was occasionally involved; sometimes only the intima and inner part of the media, and sometimes the adventitia and the outer part of the media. A nutritional vessel of the venous wall was occasionally found in the center of such a focus. The infiltrates were chiefly composed of mononuclear round cells, lymphocytes, monocytes, and histiocytes, intermingled with polymorphonuclear leukocytes. Where the infiltration extended to the endothelial surface, the endothelial lining usually was preserved but was somewhat elevated and pushed forward into the lumen. Only occasionally the endothelial lining was interrupted. But in no instance did the endothelial cells themselves show any proliferation or swelling. They were small and flat and had regular nuclei as usual. In no case was there any sign of the presence of a thrombus above such an infiltrated focus. Even when in the same vein a small thrombus was found, it was not in connection with such a focus. In one rabbit of the serum series, just the basis of a valve of the jugular vein was markedly infiltrated by leukocytes. This infiltrated focus was separated from the general inflammatory reaction in the area of the operation. The endothelium of the vein was preserved though the infiltration was just contiguous to it. At the surface the endothelium was smooth, and there was no trace of a thrombus above this acutely inflamed focus. Acute inflammation of this type is obviously pro-

duced by the reinjection, while the chronically inflamed foci may depend on one of the preparatory intravenous injections. In one of the latter instances, the histologic examination of the heart revealed in the adventitia of a coronary artery a similar inflamed focus and a circumscribed chronically inflamed subendothelial area at the beginning of the aorta.

We consider it significant that the control rabbits revealed absolutely the same endothelial "proliferations." Furthermore, these could be found in the same stage of development and in the same degree seven, twenty-four and forty-eight hours after the operation and reinjection. Even the rabbit killed eight days later did not show any sign of further progression.

The five control rabbits which were treated with antigen only once exhibited, in addition to the exposure and narrowing of the vein, distal to the site of the ligature, thrombi which were on the average not smaller than those of the immunized rabbits.

COMMENT

On the basis of our own experiments we cannot longer accept the findings of Dietrich and Schröder as evidence of the truth of Dietrich's theory that progressive thrombosis of the large veins is an allergic phenomenon produced by the active reaction of their highly sensitized endothelium to specific or even unspecific antigen carried in the blood. We found all the morphologic changes of the endothelial lining of the veins claimed by Dietrich and Schröder to be signs of proliferative reactivity of the endothelium in sensitized animals. But we could show that all these findings were deceptive. There was no real endothelial proliferation or morphologic evidence of reactivity at all. This could be proved by the fact that the morphologic changes of the endothelium were not progressive but presented the same appearance at seven, twenty-four and forty-eight hours after the exposure and narrowing of the veins and the reinjection of the antigen. There was no difference in the endothelial changes when the immunized rabbits were given reinjections of an antigen other than that of the preparation. Finally we obtained the same degree of "endothelial proliferation" in absolutely unprepared animals which had received merely one injection of bacteria following the narrowing of the veins. Therefore, the endothelial changes must be considered degenerative. Proliferation is imitated by local folds of the endothelium produced by the artificial narrowing of the veins and the local contraction of the musculature in those areas. Leukocytes of the blood deposited at the surface of this folded and slightly injured endothelium strengthen the false impression of active endothelial proliferation.

Under the influence of Dietrich's publications, Zschau also described similar endothelial changes in narrowed veins of rabbits repeatedly treated with caseosan (a product which is essentially a 5 per cent solution of casein) as active proliferations. But since no further evidence is brought forth for that theory, we must also consider these changes

merely degenerative. Ushiro [17] produced thrombi in rabbits by repeated intravenous injections of the juice of lung tissue. Five days after the last injection, he found endothelial proliferations in areas where thrombi had been formed. However, we must consider those endothelial changes the beginning of an organization tissue elicited by the thrombus itself unless the contrary can be proved. The view derived from our own experiments that the endothelium of the large veins in allergic animals does not react actively to the injected antigen in a morphologically recognizable manner is confirmed by Ewald. He repeated the experiments of Dietrich but without exposure and narrowing of the veins. Since he could not find any active endothelial changes in the venous endothelium of highly immunized rabbits, he considered the changes obtained by Dietrich and his collaborators degenerative sequelae of the operation. Neither could Apitz [18] find any sign of an active endothelial proliferation in the veins or in the heart in highly immunized rabbits or in rabbits in which small thrombi were produced in the veins or in the heart in the course of the Shwartzman phenomenon. The same is shown by Gerber.[18] Our view is further strongly supported by the results obtained from the postmortem examination of highly immunized horses which were used as donors of immune serum for periods of as long as from one to seven years and which were kept all this time on a high level of specific immunity. Paltauf,[19] Arndt,[20] Bieling,[21] Wadsworth, Hyman and Nichols [22] and Pallaske [23] reported observations at autopsies on a large number of such horses. Degenerative changes in the liver, kidney and heart, amyloidosis, for example, chronic myocarditis and endocarditis, and proliferation of the reticulo-endothelium in the liver, were usually encountered, but no proliferations of the endothelium in large peripheral veins or in the heart or thrombi in their veins were reported. Pallaske especially examined the large peripheral veins of such horses in this connection, with an entirely negative result.

Dietrich and Schröder also described in man changes of the endothelium of the large femoral veins just in the areas where thrombosis usually arises, which they considered similar to those obtained in their experiments. Since they found such changes specifically in the veins of persons who had died in the course of infectious diseases, they

17. Ushiro.: Deutsche Ztschr. f. Chir. **245**:16, 1935.

18. Gerber, I. E.: Am. J. Path. **11**:843, 1935; Arch. Path. **21**:776, 1936.

19. Paltauf, in Sternberg, C.: Verhandl. d. deutsch. path. Gesellsch. **26**:254, 1931.

20. Arndt, H. J.: Verhandl. d. deutsch. path. Gesellsch. **26**:243, 1931.

21. Bieling, R.: Verhandl. d. deutsch. path. Gesellsch. **26**:251, 1931.

22. Wadsworth, A.; Hyman, L. W., and Nichols, R. R.: Am. J. Path. **11**: 419, 1935.

23. Pallaske, G.: Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch. **7**:73, 1934.

regarded these findings as further and essential evidence for their theory of the importance of active allergic endothelial proliferation in the pathogenesis of progressive thrombosis. But von Lucadou,[24] with whom Aschoff [15] agreed, showed that these venous changes were dependent only on the age of the deceased persons and had nothing to do with allergy or endothelial sensitivity.

In our experiments we made the striking but not absolutely unexpected observation that degenerative or inflammatory lesions of the endothelium of large veins are not necessarily followed by thrombi, not even by strictly localized thrombi. We usually found a small thrombus above an injured segment of a venous wall when the injury was severe enough to produce morphologically recognizable necrosis in the venous wall, as happened in the instances when the vein was entirely tied off by the ligature. There usually was a small focus of necrosis in the area directly beneath the ligature, often demarcated by a leukocytic wall, and here in most cases a small thrombus was adherent. But merely slight degenerative changes of the endothelium or small areas denuded of endothelium were, even in highly immunized rabbits, not sufficient to produce local thrombi. This was especially obvious in the venous segments proximal to the ligatures. Such small endothelial defects were covered only by leukocytes deposited from the blood stream. Furthermore, even at the endothelial surface of the circumscribed focus in the wall of the jugular vein which was densely infiltrated by leukocytes or mononuclear round cells, there was no trace of a thrombus. The facts learned by long experience in surgical treatment of blood vessels as they recently were revealed by Stich [25] also showed that a simple, slight local inflammation which necessarily accompanies the transplantation of a blood vessel did not as a rule produce thrombosis. From earlier microscopic studies on blood vessels in the living animal, we [26] learned that even slight local irritations of the tissue or the blood vessels themselves were sufficient to induce local massing of numerous leukocytes in the small veins and the beginning of their migration into the tissue within a relatively short time. But a reaction of the platelets within the flowing blood could not be so easily produced unless specific conditions were provided. The relatively prompt reaction of the blood leukocytes was usually a sufficient protection for the rest of the flowing blood against the sequelae of slight injuries to the tissue and the blood vessels, apparently by withholding or neutralizing substances which in the tissue had arisen as sequences of the injuries. These observations show that leukocytic infiltration of a venous wall, in other words, slight

24. von Lucadou, W.: Ztschr. f. Kreislaufforsch. **25**:785, 1933.

25. Stich, R.: Arch. f. klin. Chir. **183**:300, 1935.

26. Tannenberg, J.: Frankfurt. Ztschr. f. Path. **31**:351, 1925; Deutsche med. Wchnschr. **58**:936, 1932.

phlebitis by itself, should not be regarded as very significant for the pathogenesis of thrombosis. When the local injury to the venous wall is so severe that the local inflammatory reaction is unable to bind its products, then a localized thrombus usually occurs, as we found it, for example, in our present experiments, above localized necrosis of the venous wall. As to the nature of the acutely or chronically inflamed foci of the jugular vein which we found in our serum and pneumococcic series, we considered it most probable that they represented a local reaction to the injected antigen, even though strict morphologic evidence cannot be brought forth. The following reasons support this consideration: The lesions in these foci are quite comparable to the granulomatous inflammatory lesions described as allergic in the wall of coronary arteries of rabbits repeatedly treated with horse or hog serum (Klinge,[27] Vaubel,[28] Junghans[29]). In one instance we also found, together with chronically inflamed foci of both jugular veins, such foci in the adventitia of a coronary artery, involving the media, and a chronic circumscribed subendothelial infiltration at the beginning of the aorta. Furthermore, we found in a high percentage of our immunized series, in the pulmonary arteries and in the heart, small inflammatory lesions which we also considered the result of the repeated injections of antigen, since we only occasionally found such lesions in a series of over fifty rabbits which were given intravenous injections merely once. But in this connection we do not intend to discuss more in detail the question of whether or not they are the result of an allergic inflammation. Here the main interest is in the fact that these densely inflamed foci did not produce any thrombotic reaction in the lumen of the vein. To avoid misunderstanding, however, we add that we do not consider the morphologic appearance of these inflamed foci by itself pathognomonic or specific for allergic inflammation. Chronically inflamed foci like these are encountered by us and undoubtedly many other pathologists in veins of chronically inflamed organs in man, in cases without relationship to allergy. But in the present experiments on rabbits all the circumstances under which we encountered them made it most probable that they were the result of a reaction to the injected antigen.

SUMMARY

The influence of allergy on the development and progression of thrombosis is studied specifically with a view to the significance of allergic endothelial changes in the larger veins. Three groups of rabbits

27. Klinge, F.: Beitr. z. path. Anat. u. z. allg. Path. **83**:185, 1929; Virchows Arch. f. path. Anat. **279**:438, 1930.
28. Vaubel, E.: Beitr. z. path. Anat. u. z. allg. Path. **89**:374, 1932.
29. Junghans, E.: Beitr. z. path. Anat. u. z. allg. Path. **92**:467, 1934.

were prepared by nine intravenous injections of antigen (pneumococci, streptococci and sheep serum, respectively). From seven to eighteen days later the right jugular and femoral veins in each animal were exposed and narrowed and an intravenous reinjection was made into the corresponding ear vein.

As a result, however, merely local thrombi were obtained, not larger than those in the nonimmunized controls. Only a single rabbit, which in addition presented a progressive, widely spread chronic nephritis, exhibited a kind of progressive thrombosis.

In the narrowed segments of the veins endothelial changes morphologically similar to active proliferations were observed. But their failure to show progression seven, twenty-four and forty-eight hours after the operations and the occurrence of similar changes in the controls showed that to interpret them as an allergic, active endothelial reaction would be erroneous. Serial sections revealed that these changes were produced by folding of the endothelium in the narrowed segments, superficial degenerative changes of the endothelium and deposits of blood leukocytes at the injured areas.

Slight degenerative changes of the endothelium as well as diffuse or localized inflammatory infiltrations of the venous wall proved to be insignificant for the formation of thrombi even in highly sensitized animals unless morphologically recognizable necrosis or break-down of tissue was found, the products of which could not be localized or neutralized by a primary leukocytic and subsequent mononuclear round cell reaction.

EFFECT OF ROENTGEN RAYS ON THE BLOOD UREA OF RATS IMMUNE TO JENSEN'S SARCOMA

ISABELLA H. PERRY, M.D.
SAN FRANCISCO

In 1925 Dodds, Lawson and Mottram [1] reported that the blood urea of rats immune to Jensen's sarcoma is reduced about 50 per cent after the administration of an erythema dose of roentgen rays, while that of normal and of tumor-bearing animals is unchanged. Although this is

Observations on Blood Urea of Rats Treated with an Erythema Dose of Roentgen Rays

Blood Urea, Mg. per Cent		Days After Treatment	Percentage Difference
Before Treatment	After Treatment		
	Eleven Rats Immune to Jensen Sarcoma		
26.5	11.4	2	>57
19	9	4	53
21.3	10	3	51
16.5	8.6	6	49
28.8	15	8	48
16.5	9.4	6	44
17.6	10.2	5	43
15	8.8	5	42
24.5	15	3	39
17.7	11.4	2	36
15	9.3	6	35
			Av. >45
	Four Control Rats		
14.9	16.2	3	< 8
17	14.5	3	>15
14	13.5	6	..
24	26.7	6	<10
			Av. < 0.7

the only concrete chemical change that has been reported in such immunity, it has attracted little notice. Six years later Dodds [2] refers to this observation again. He suggests no explanation of it.

My associates and I saved all the rats in our colony that were immune to Jensen's sarcoma, to repeat Dodds' work. The procedure was improved in that we were able to determine the blood urea on the same animals before and after treating them with roentgen rays, by bleeding

From the Department of Pathology, University of California Medical School.

1. Dodds, E. C.; Lawson, W., and Mottram, J. C.: Biochem. J. **19**:750, 1925.
2. Dodds, E. C.: Am. J. Cancer **15**:2765, 1931.

from the external jugular vein and using the Tauber-Kwartin [3] modification of Grueskin's micromethod for determining blood urea. All immune rats were reinoculated with Jensen's sarcoma at least twice after the first failure of the tumor to take. The controls were inoculated with the tumor, and the chemical examinations were made while the tumor was growing. Each rat received the application of the roentgen rays while confined in a small cylindric wire cage about the size of the animal. The whole body was treated. No filter was used. The dose was 875 roentgens with a focal skin distance of 8 inches (20 cm.); the exposure was for five minutes.

The results are shown in the table. They substantiate Dodds' work.

3. Tauber, H., and Kwartin, B.: J. Lab. & Clin. Med. **15**:260, 1929.

PATHOLOGY OF THE PROSTATIC UTRICLE

ROBERT A. MOORE, M.D.
NEW YORK

The prostatic utricle has been the object of few pathologic investigations since it was first described. A variety of names have been applied to it: utriculus masculinis, prostatic utricle, sinus pocularis and male vagina or uterus.

The utricle is the male structure derived from the müllerian duct and is in general analogous to the vagina in the adult female. This relationship is well shown in pseudohermaphrodism, as in the case observed by Young and Cash,[1] in which the utricle was long and ascended the posterior walls of the prostate and bladder as a solid cord.

In this paper, observations on the pathologic changes in the prostatic utricle in 678 cases, as seen in step sections of the prostate, are reported. Begg [2] stated that the utricle may be entirely absent, but in this material it was always present. It varied in length from less than 4 mm. (the distance between step sections) to between 12 and 16 mm. (fig. 1 *A*). There was no correlation between the apparent length and the age of the patient.

SENILE INVOLUTION

In a process entirely analogous to that which has been described in the prostate [3] the epithelial and connective tissue elements of the utricle undergo alteration with increasing age.

In the adult of the third and fourth decade of life the utricle is lined with tall columnar epithelium similar to that in the prostate (fig. 1 *B*). This epithelium is thrown into occasional papillae and numerous small evaginations. Within the lumens, a small amount of granular acidophilic débris is present. The luminal border of the epithelium is irregular, and in some cells a direct continuity between the cytoplasm and the débris

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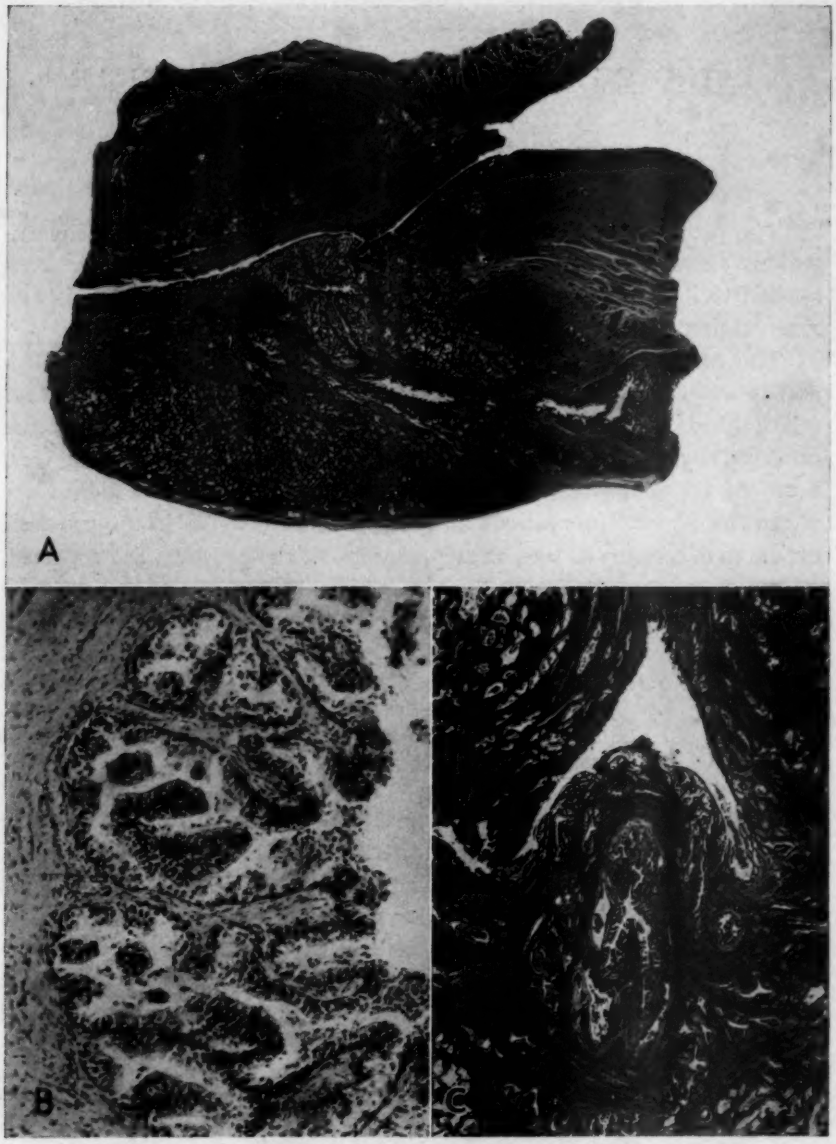
The material for this investigation was collected in Vienna while the author served as a Fellow of the National Research Council. Assistance in the preparation of the slides was given by the Committee on Grants-in-Aid of the National Research Council.

From the Department of Pathology, New York Hospital and Cornell University Medical College, New York; Institute of Pathology, Western Reserve University, Cleveland, and Das pathologisch-anatomische Institut des Krankenhauses der Stadt Wien.

1. Young, H. H., and Cash, J. R.: J. Urol. **5**:405, 1921.
2. Begg, R. C.: Brit. J. Urol. **1**:237, 1929.
3. Moore, R. A.: Am. J. Path. **12**:599, 1936.



EXPLANATION OF FIGURE 1

A, longitudinal section through the midline of the prostate; × 7. The anterior, posterior and middle lobes of the prostate are shown clearly. The utricle is a richly branching, demarcated mass of glands below the slight elevation in the urethra.

B, the utricle of a man, 30 years of age, with the characteristic columnar epithelium which is thrown into numerous papillae; × 150.

C, cross-section of the utricular region; × 22. Note that there is a capsule of smooth muscle which separates the utricle from the prostate.

may be seen, presumably a process of apocrine secretion. In many areas a continuous layer of flattened basal epithelial cells can be demonstrated. Immediately beneath the epithelium is a thin layer of collagenous connective tissue. The whole is embedded in a stroma of connective tissue and smooth muscle, which is entirely distinct from the stroma of the prostate and separated from it by a pseudocapsule (fig. 1 *C*). Not infrequently there is a definite longitudinal smooth muscle bundle within this capsule.

In the early part of the fifth decade of life and not infrequently in the latter part of the fourth decade, the epithelium and stroma show definite changes from this picture (fig. 2 *A*). The epithelium is more cuboid or flattened, and a basal layer of cells is not demonstrable. In many areas the epithelium is many cells thick and resembles the transitional type. Keratinization has not been observed under normal conditions. The cell walls are clearly defined, and there is no indication of a secretory process. Papillae are not present, and there is an apparent decrease in the number of evaginations along the wall of the larger utricular cavity. The muscular tissue of the stroma is markedly reduced, and the connective tissue collar about the glands is thicker and hyalinized. Not infrequently the connective tissue forms small bulbous masses which project into the lumen.

In contrast to the process of senile involution in the prostate, that in the utricle occurs at an earlier age, from 35 to 40 years, and is complete within ten years.

The physiologic correlation of these anatomic changes must await further studies of the "sex hormones." Zuckermann and Parkes [4] found that androsterone, dihydro-androsterone and a commercial androgenic preparation from male urine had no effect on the utricle of the immature monkey (Macacus rhesus). Further investigations on the presence of estrogen in the male urine [5] and the relation to age may be informative.

CORPORA AMYLACEA

With the appearance of the senile changes described corpora amylacea are found in the lumens of the utricular evaginations. With eosin they are slightly acidophilic and homogeneous or finely granular. They are small and rarely show concentric laminations. Central softening, calcification and pigmentation are uncommon secondary changes. Castaño [6] described utricular corpora and concluded that they were composed largely of derivatives of cholesterol.

4. Zuckermann, S., and Parkes, A. S.: Lancet **1**:242, 1936.
5. Fee, A. R.; Marrian, G. F., and Parkes, A. S.: J. Physiol. **67**:377, 1929.
6. Castaño, E.: Rev. de especialid. **2**:1007, 1927.

EXPLANATION OF FIGURE 2

A, the utricle in a man 52 years of age; × 150. The epithelium is low cuboid and in places stratified. Compare with figure 1*B*.

B, the utricle in a man who was castrated five years before death; × 150. There are no evaginations, and the epithelium is of the transitional type.

C, squamous metaplasia of the utricular epithelium in a man with metastatic carcinoma of both testes and of the pituitary gland; × 150.

D, macroscopic appearance of a cross-section of a cyst of the prostatic utricle. The ejaculatory ducts are visible as darker semilunar-shaped slits on the lateral sides of the cyst.

E, section through the extreme height of the verumontanum in a case of utricular cyst; × 46. Note that the cystic cavity bulges into the urethra.

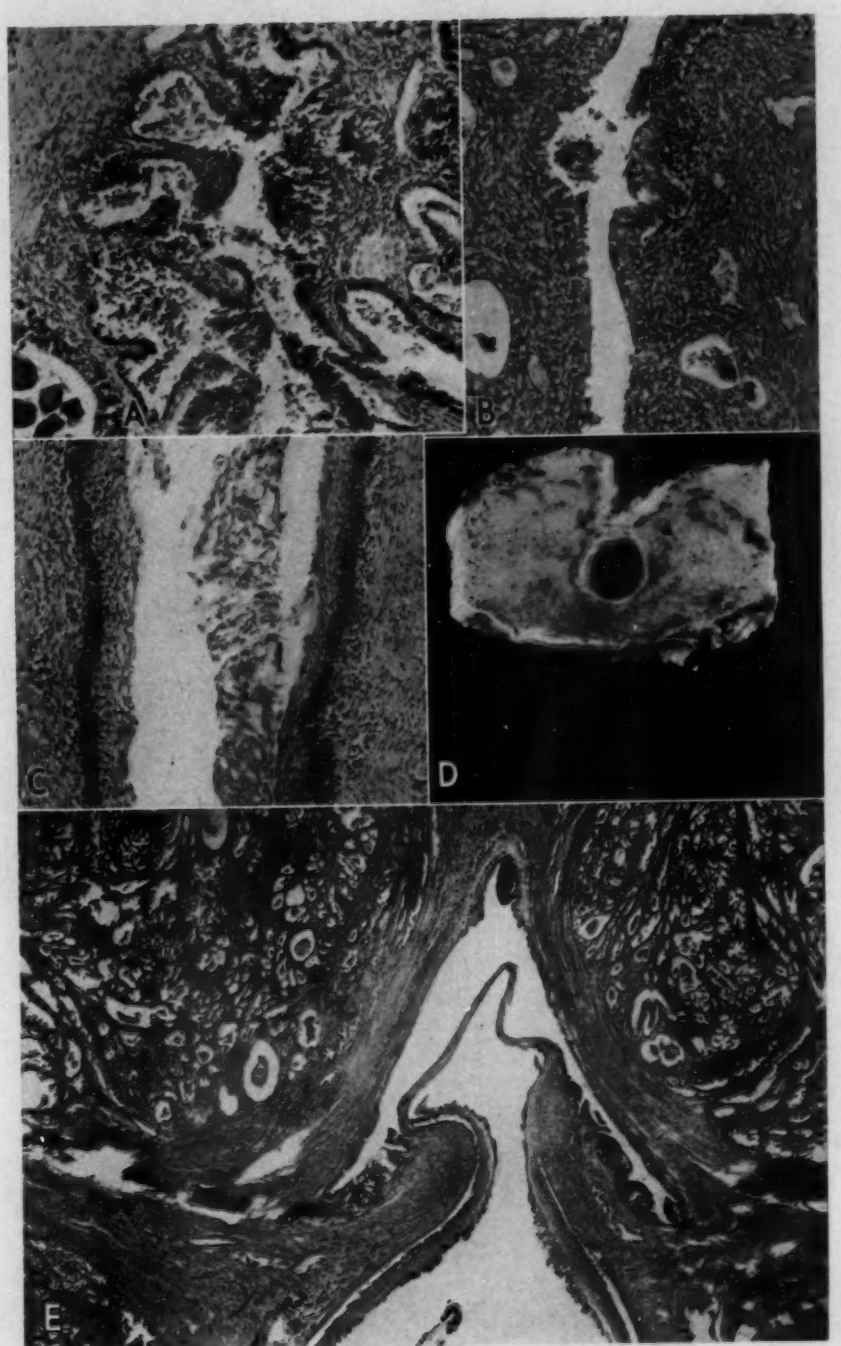


Figure 2

INVOLUTION OF CASTRATION

The sections in a case of castration, made five years before death, have been studied. The utricle is small and lined by a many-layered transitional type of epithelium, which is sharply separated from the surrounding stroma (fig. 2 *B*). There is no evidence of secretion, and no corpora are present. This finding is in agreement with the published reports on the prostate as studied in eunuchs and eunuchoids.[7]

SQUAMOUS CELL METAPLASIA

In the sections in one case, the utricle is lined by a many-layered squamous epithelium with typical intercellular bridges (fig. 2 *C*). The subepithelial tissues are infiltrated with a few lymphocytes, and similar cells are between the epithelial cells. The prostate shows the usual structure of that of a person of 45 years of age. The patient died of metastases from a carcinoma of the stomach, which had caused partial anatomic destruction of both testes and the pituitary gland.

Schlachta [8] reported metaplasia of the epithelium of the utricle to *Pflasterepithel* in new-born infants. Zuckermann and Parkes [4] produced squamous metaplasia of the utricle by injecting an estrogenic substance, theelin, into immature monkeys (Macacus rhesus). The probable absence of both testicular and hypophysial hormones in the case reported here and the observations of Zuckermann and Parkes are significant in the light of the general theory of intersexuality of Goldschmidt [9] and the application of the theory to the prostate by Moszkowicz.[10] The latter held that in presenility, the decreased activity of the testes allowed those parts of the prostate which were more female in origin to undergo hyperplasia.

CYSTIC DILATATION

The first studies of pathologic changes in the utricle were by Englisch,[11] on cystic dilatation. He found 5 examples of this condition in 70 new-born and young infants. The present material does not include a similar age group. However, in adults, 7 instances of dilatation have been observed. The ages were 56, 59, 61, 68, 70, 78 and 85 years. There was no other significant finding in the autopsies to set these cases into a group. The condition is readily recognized macroscopically (fig. 2 *D*). The cavity is usually from 20 to 30 mm. in length and from 7 to 15 mm. in diameter, and it is filled with a clear viscid fluid, which coagulates to a firm gel on fixation with formaldehyde. The

7. Altman, F.: Virchows Arch. f. path. Anat. **276**:455, 1930.
8. Schlachta, J.: Arch. f. mikr. Anat. **64**:405, 1904.
9. Goldschmidt, R.: Die sexuellen Zwischenstufen, Berlin, Julius Springer, 1931.
10. Moszkowicz, L.: Virchows Arch. f. path. Anat. **284**:428, 1932.
11. Englisch, V.: Abstr., Jahresb. ü. d. Leistung. d. ges. Med. **8**:191. 1873.

internal wall is smooth, and the ejaculatory ducts are compressed peripherally, while in cross-section they appear as elongated semilunar structures. The cavity extends into the verumontanum, which is pushed anteriorly and caudally so that the lumen of the urethra is encroached on and minor urinary difficulty is to be expected. The pressure on the ejaculatory ducts was the more important effect in the case reported by Lubash,[12] in which a 25 year old man complained of impotence for two years and was entirely relieved after catheterization of the utricle and removal of 8 cc. of milky white fluid.

Microscopically the cavity is lined by low columnar or cuboid epithelial cells, with low papillae. There are no invaginations as in the normal utricle. The surrounding stroma contains a few muscle fibers. In one case, sections through the entire verumontanum show that the cavity is sharply separated from the urethra, with no epithelial structure between the two (fig. 2*E*). There is no cellular infiltration, and the lesion may be either a congenital anomaly or a healed inflammatory atresia of the orifice. The higher incidence of dilatation in new-born infants as compared with that in adults found by Englisch [11] indicates that the lesion in the former is transitory and due to edema or related phenomena in the neonatal period. Jenkins, Deming and van Wagenen [13] and Horst [14] stated that the distal prostatic urethra in the male corresponds to the vagina in the female, and it is possible that the hormones of the mother, which act on female structures, bring about the changes in the new-born infant. Wesson [15] in 1925 collected 6 published cases of cystic dilatation of the utricle in adults.

TUBERCULOSIS

In 1 of 22 cases of genito-urinary tuberculosis there were active lesions in the utricle. There was associated tuberculosis of the kidney, urethra, bladder and prostatic urethra, and it seems likely that the utricular disease was secondary to that in the urethra. Hesse [16] mentioned a case of utricular tuberculosis but gave no details. Microscopically, the picture is entirely typical of tuberculosis and need not be described in detail.

PYOGENIC INFLAMMATION

Begg [2] reported a case in which the utricle was dilated with pus and projected into the urethra as a smooth eminence. Belfield [17] described

12. Lubash, S.: Am. J. Surg. **7**:123, 1929.
13. Jenkins, R. H.; Deming, C. L., and van Wagenen, G.: New England J. Med. **211**:569, 1934.
14. Horst, I.: Frankfurt Ztschr. f. Path. **46**:202, 1933.
15. Wesson, M. B.: J. Urol. **13**:605, 1925.
16. Hesse, F. A.: Centralbl. f. d. Grenzgeb. d. Med. u. Chir. **17**:297, 1913.
17. Belfield, W. T.: J. A. M. A. **22**:574, 1894.

several clinical cases in which there was evidence of acute or subacute inflammation of the utricle.

A distinction should be made between urethritis with inflammation of the subepithelial tissues of the verumontanum and utriculitis, in which the inflammation is within the lumen and tissue about the utricle. There were 5 examples of the latter type among the 678 prostates examined. The ages were 50, 74, 77, 85 and 91 years. In all the cases there were associated prostatitis and cystitis, and in 4 of the 5 examples mentioned there was benign enlargement of the prostate. The inflammation in all cases was characterized by lymphocytic infiltration with only an occasional polymorphonuclear leukocyte. There was no conspicuous exudation into the lumen as in the case of Begg.[2]

UTRICLE IN BENIGN ENLARGEMENT OF THE PROSTATE

In view of the theory that intersexuality is the cause of benign enlargement [10] it is of considerable interest to study the utricle in this disease. It is at once apparent that there is no consistent finding, although the lesion described as senile metaplasia is more conspicuous and advanced in patients with benign enlargement than in persons of the same age groups free from the disease. In no instance is there metaplasia of a true squamous character with prickle cells.

SUMMARY

The prostatic utricle undergoes senile involution in much the same manner as the prostate, but its involution occurs in the fifth decade of life rather than in the sixth.

A case of squamous metaplasia of the epithelium of the utricle with partial destruction of the testes and pituitary gland is reported. The change in such a case is identical with that induced by an estrogenic substance, theelin, in immature male monkeys (Macacus rhesus).

Castration induces involution in the utricle as well as in the other male accessory sexual organs.

Cystic dilatation of the utricle is a not uncommon disease and may be responsible for a rare case of impotence or of slight urinary difficulty.

Tuberculosis of the utricle is rare. It occurred in only 1 of 22 cases of tuberculosis of the genito-urinary organs in this series.

Utriculitis, as distinguished from inflammation of the subepithelial tissue of the verumontanum, was observed in only 5 cases and is clearly a complication of cystitis and prostatitis, usually with benign enlargement.

There are no regularly observed changes in the utricle in association with benign enlargement.

Case Reports

SARCOMA OF THE UTERUS

J. MARSHALL NEELY, M.D., LINCOLN, NEB.

While carcinoma of the uterine fundus is comparatively common, sarcoma of the uterus is extremely rare. Although Mayer [1] is usually given credit for having been the first to describe sarcoma of the uterus, it was recently pointed out by Carlisle [2] that Lebert, in 1845, was the first to describe this tumor microscopically. General recognition of sarcoma of the uterus dates back to the work of Virchow and Mayer in 1860.[1] Williams,[3] in 1894, contributed an excellent paper on the subject, and since that time many articles dealing with it have appeared in both foreign and American literature. Owing to the rarity of the condition, most of these articles present single case reports, although comparatively large series have been studied and described by Strong,[4] Masson,[5] Vogt,[6] Wolfe,[7] Kimbrough [8] and others. Sarcoma of the pregnant uterus [9] has been described, and both adenocarcinoma and sarcoma have been found in the same uterus.[10]

Sarcoma of the uterus constitutes about 2 per cent of all uterine neoplasms and about 5 per cent of those which are malignant.[11] According to Masson,[5] some writers have listed the frequency as high as 10 per cent and as low as 0.4 per cent. This discrepancy is undoubtedly the result of difference in the interpretation of histologic changes in fibromyoma by different pathologists.

Sarcoma of the uterus is rarely diagnosed clinically. In cases in which it is correctly diagnosed it is usually found in rapidly growing fibromyoma. According to Wolfe,[7] the diagnosis may be made by curettage in about 50 per cent of the cases. There is nothing about the clinical history or physical findings to separate sarcoma definitely from adenocarcinoma of the uterine fundus.

There are almost as many classifications of this tumor as there are writers on the subject. In general, sarcoma of the uterus may be divided into that which arises in preexisting fibromyoma and that which does not. That which is primary, or does not arise in fibromyoma,

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From the Lancaster County Medical Museum.

1. Needles, Robert J.: Am. J. Cancer **19**:364, 1933.
2. Carlisle, W. T.: Illinois M. J. **70**:227, 1936.
3. Williams, J. W.: Am. J. Obst. & Gynec. **29**:721, 1894.
4. Strong, L. W.: Am. J. Obst. & Gynec. **71**:230, 1915.
5. Masson, J. C.: Am. J. Obst. & Gynec. **5**:345, 1923.
6. Vogt, M. E.: Am. J. Obst. & Gynec. **5**:423, 1923.
7. Wolfe, S. A.: Am. J. Obst. & Gynec. **23**:232, 1932.
8. Kimbrough, A. J.: Am. J. Obst. & Gynec. **28**:723, 1934.
9. DerBrucke, M. G.: Am. J. Obst. & Gynec. **26**:457, 1933.
10. Goldstein, M. T.: Am. J. Obst. & Gynec. **30**:143, 1935. Klaften, E., and Navrotil, E.: Zentralbl. f. Gynäk. **58**:2170, 1934.
11. Carlisle.[2] Wolfe.[7]

may again be subdivided into the subserous, the intramural and the submucous type according to the location, or into the diffuse and the circumscribed type according to the gross characteristics. Botryoid sarcoma, a tumor of the cervix which occurs most frequently in children, will not be considered in this discussion. Histologically it is usually divided into the spindle cell, the round cell and the giant cell variety, although polymorphous cell sarcoma and mixed sarcoma have also been described.

REPORT OF A CASE

The material which constitutes the basis for this communication was obtained from the curettings and surgically removed uterus of a woman aged 58 who for a period of one year had intermittent attacks of metrorrhagia. This was accompanied by backaches, cramps and vaginal discharge. The uterine fundus was enlarged and soft. The blood showed 4,170,000 red cells per cubic millimeter, with hemoglobin 83 per cent, 6,530 white cells and a negative Wassermann reaction.

The diagnostic curettage, done immediately after admission to the hospital, revealed an abundant quantity of endometrial tissue, which was soft, gray-yellow, friable and accompanied by very little blood clot. The tissue was fixed in solution of formaldehyde U. S. P. and Zenker's solution containing solution of formaldehyde, and paraffin sections were stained with hematoxylin eosin and Masson's trichrome stains.[11a] These sections showed a rather anaplastic mesenchymal growth, the cells occurring in almost solid culture. They varied considerably in size and shape, many being polyhedral and others showing long tail-like processes. Mitosis was frequent. Many multinuclear giant cells were seen in all of the sections. The Masson trichrome stains did not reveal any fibroglial fibrils, although myoglial fibrils were seen. The supporting stroma was quite delicate. No cross striations were seen.

On the basis of these findings a diagnosis of myosarcoma of the uterus was made, and the patient received two series of treatments with roentgen rays of high voltage. After this, total hysterectomy and bilateral salpingo-oophorectomy were done.

The uterus was slightly enlarged, and there was a slight boggy prominence near the fundus posteriorly. On cut section, this was found to be an ill defined, irregular, soft, yellowish gray tumor measuring 3 cm. in the greatest diameter. It extended through the endometrium at one point, producing a small nodule on the endometrial surface. There was also a typical polyp in the fundus, which apparently had no relationship to the intramural growth. The remainder of the endometrium, except at the point of infiltration, showed nothing of note. The fallopian tubes, ovaries and cervix were not remarkable.

Several sections of the tumor stained with hematoxylin eosin and Masson's hemalum-erythrosin-saffron stains showed a histologic character somewhat different from that of the material obtained by curettage. The cells were more polymorphous, mitosis was much less frequent, there were many more and larger giant cells, and there were large areas of necrosis. The necrosis was probably at least partly due to the preoperative high voltage roentgen therapy, although, according to Williams,[3] necrosis is a characteristic of the circumscribed intramural form of uterine sarcoma. The individual tumor cells were large, ribbon-like, and contained large oval vesicular nuclei. In the sections stained with Masson's trichrome aniline blue method myoglial fibrils were seen at the end of the cells. In other parts

11a. Masson, P.: J. Tech. Methods **12**:75, 1929.

of the tumor the histologic picture was quite different. Here the tumor cells were small and round with very little cytoplasm. They were supported by a delicate connective tissue stroma. In the sections where there was considerable necrosis many of the histiocytes were laden with yellow pigment. At the peripheral portions of the tumor which were not necrotic one might follow each step in the development of the smooth muscle cell from the undifferentiated round mother mesenchymal cell to the large, ribbon-like muscle cell. As the cell became more differentiated the cytoplasm became more abundant and the nucleus elongated. In the undifferentiated cells the cytoplasm was scanty and the chromatin of the nucleus more compact. Fibroblasts and fibrocytes were encountered but did not seem to take part in the formation of the tumor. In the sections treated with the Masson trichrome stains collagen was seen in the degenerated areas and also in thin strands among the tumor cells.

When one remembers that in the pregnant uterus new muscle cells are formed by differentiation of the small round undifferentiated mesenchymal cell found normally between the muscle bundles it seems unnecessary to assume the presence of an embryonic rest to explain the development of sarcoma of the uterus. That this undifferentiated mesenchymal cell is multipotential is evident from the occasional occurrence of a mixed tumor and osteogenic sarcoma in the uterus. Some believe that the mixed tumor arises from a wolffian duct rest in the uterus. This, however, has not been proved, and in so much as the uterus is also derived from the urogenital ridge embryologically it seems more reasonable to believe that the mixed tumor or Wilms' tumor represents difference in the differentiation of the same multipotent undifferentiated mesenchymal cell.

Multinuclear giant cells are described in practically every report of sarcoma of the uterus thus far published. In this case they were found in both the curettings and the tumor. Since giant cells are practically always found in sarcoma of the uterus I believe it is wrong to use the term "giant cell sarcoma" as designating one of the subvarieties. The giant cells found in myosarcoma of the uterus are undoubtedly of histiocytic origin.

A small group of tumors have been separated from myosarcoma by Needles [1] and described as polymorphous sarcoma of the uterus. There seems to be little reason for this segregation in view of the characteristic cell variation in all uterine sarcoma. There is marked variation in the size and shape of the cells in sarcoma of the uterus not only from case to case but also in different portions of the same tumor. Polymorphism is a characteristic of sarcoma of the uterus in general and should not be used as a criterion for subdivision of the general group.

The degree of malignancy of sarcoma of the uterus may be judged somewhat by the histology. When the tumor shows a large number of giant cells it is said to be relatively benign and it rarely metastasizes.[5] The form designated as spindle cell sarcoma is thought to be more malignant and more common. The prognosis of sarcoma arising in preexisting fibromyoma is about three times better than for sarcoma

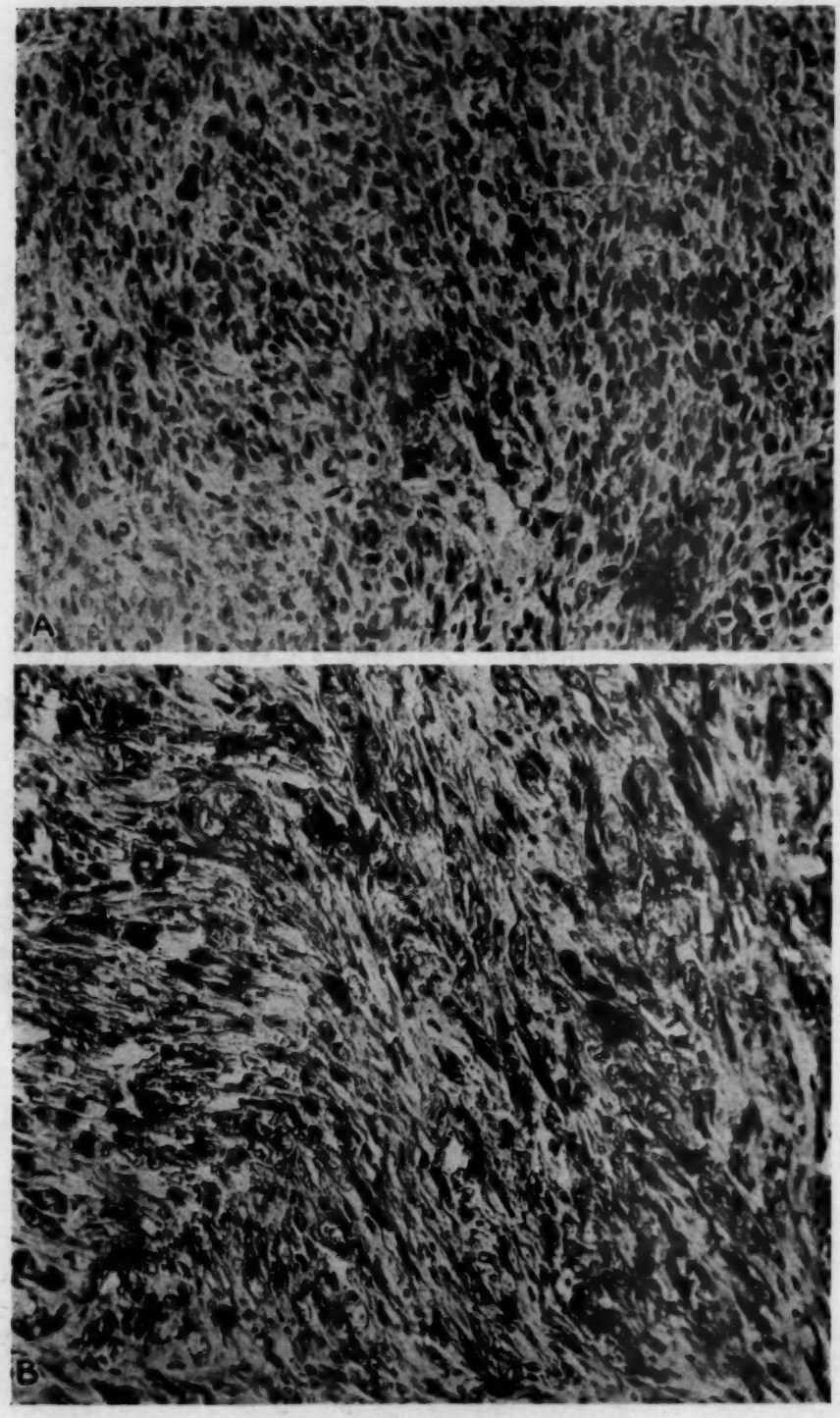

Fig. 1.—*A*, low power photomicrograph of uterine curettings, showing type of spindle-shaped tumor cell; *B*, low power photomicrograph showing character and arrangement of the tumor cells; section of an intramural tumor.

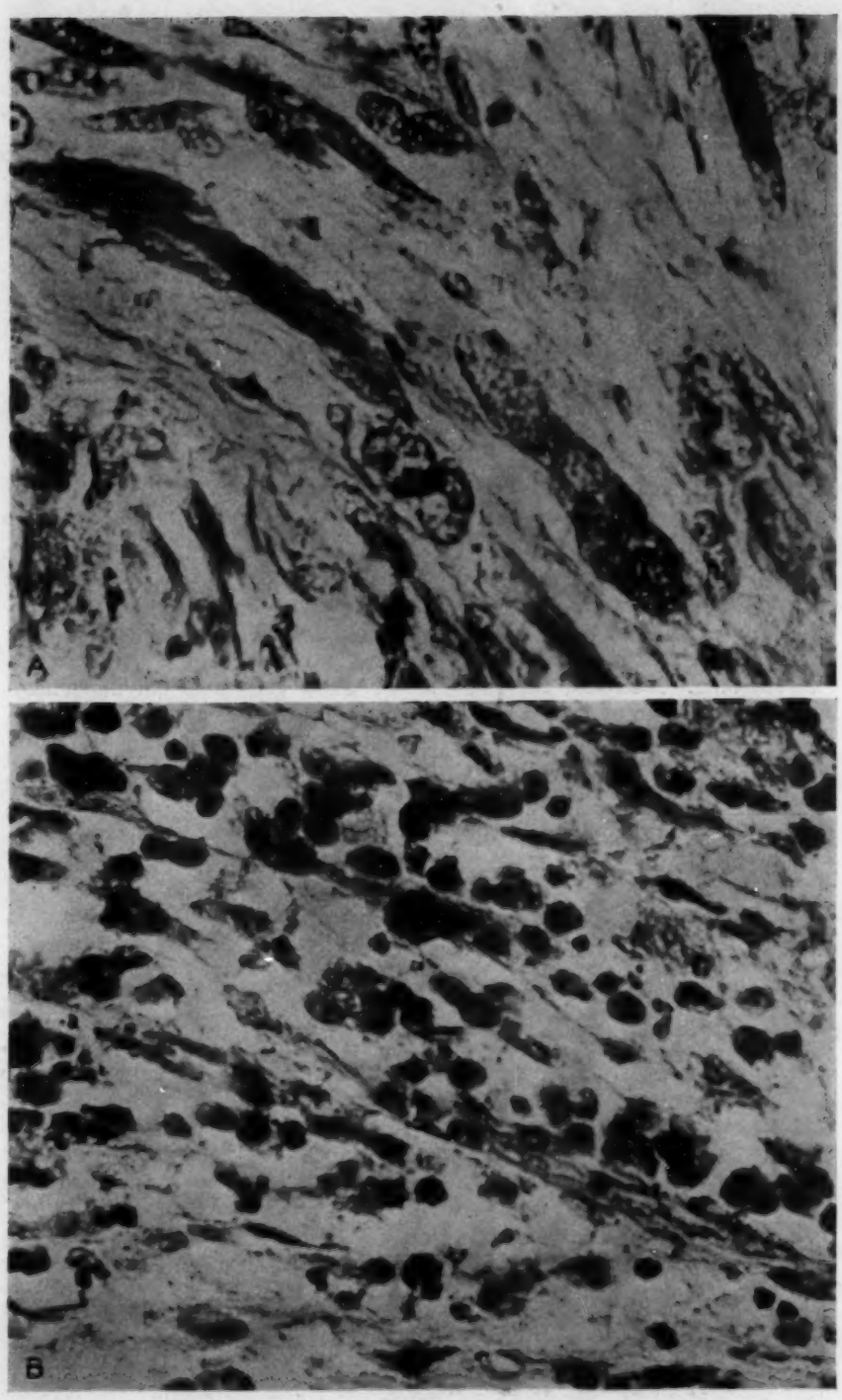

Fig. 2.—*A*, high power photomicrograph of uterine tumor, showing ribbon-like cells; *B*, high power photomicrograph of a more undifferentiated portion of the tumor, showing cells that are round and almost lymphoid.

which is primary.[12] The number of mitotic figures is also a rough index of the degree of malignancy.[13]

In a series of thirty cases reported by Vogt [6] only in eight could the sarcoma be traced to previously existing fibromyoma. As pointed out by Reel and Charlton,[14] in many instances it is difficult to determine whether or not there has been preexisting fibromyoma. The histogenesis of uterine sarcoma is undoubtedly the same whether the sarcoma arises in fibromyoma or not. Metaplasia in the usual sense of the word probably plays no part. There is no evidence that a well differentiated smooth muscle cell or fibrous connective tissue cell ever becomes dedifferentiated, changing its morphologic characteristics. The progenitor of sarcoma of the uterus is undoubtedly the undifferentiated mesenchymal cell which is found in the normal uterine wall and in the interstices of ordinary fibromyoma.

The use of Masson's trichrome stains greatly facilitates the study and adds much to the histologic picture in so much as the collagen and smooth muscle are sharply delimited.

SUMMARY

A case of myosarcoma of the uterus is described. Curettage is the only accurate method of diagnosis and is positive in about 50 per cent of the cases. This case presented no evidence of preexisting fibromyoma. Necrosis, the presence of giant cells and polymorphism are characteristic of sarcoma arising in the uterus. There is no purpose in subdividing the general group into giant cell sarcoma and polymorphous cell sarcoma. The use of Masson's trichrome stains in the study of uterine sarcoma is recommended.

12. Proper, M. S., and Simpson, B. T.: Surg., Gynec. & Obst. **29**:39, 1919.

13. Moench, G. H., and Meeker, Louise H.: Am. J. Obst. & Gynec. **30**:435, 1935.

14. Reel, P. J., and Charlton, P. H.: Ann. Surg. **77**:476, 1923.

CARCINOMA OF THE BREAST WITH A CONDITION OF THE BLOOD SIMULATING CHRONIC LYMPHATIC LEUKEMIA

ANGELO M. SALA, M.D., AND ROBERT J. STEIN, M.S., NEW YORK

A leukemic condition of the blood appearing simultaneously with a malignant neoplasm is not a rare finding,[1] but carcinoma of the breast simulating chronic lymphatic leukemia is not common and in our opinion warrants a report.

REPORT OF A CASE

A 44 year old colored woman was admitted to the hospital in September 1934 with a diagnosis of chronic lymphatic leukemia involving the bones and leukemic infiltration of the left breast. The blood picture was as follows: hemoglobin (Sahli), 44 per cent; erythrocytes, 1,940,000; leukocytes, 33,400; neutrophilic myelocytes, 2 per cent; neutrophilic metamyelocytes, 6 per cent; neutrophilic polymorphonuclears, 29 per cent; eosinophilic polymorphonuclears, 1 per cent; basophilic polymorphonuclears, 1 per cent; large lymphocytes, 59 per cent; monocytes, 2 per cent; normoblasts, 1 per hundred white cells; megaloblasts 2 per hundred white cells; reticulocytes, 8 per cent, and blood platelets, 65,000.

The patient complained chiefly of dyspnea and pain in the left breast, which had been present for seven months, and of cutaneous eruptions, from which she had suffered for one year. Many petechiae were diffusely distributed over the body. The patient was obese, dyspneic and orthopneic. The right breast was large and pendulous; the axilla, normal. In the left breast there was a large hard irregular mass, about 10 by 7.5 cm., just below the nipple, fixed to the skin; there were large firm nodes in the left axilla. The liver was definitely enlarged. The diagnosis was carcinoma of the left breast with axillary and skeletal metastases.

The blood picture was: hemoglobin (Dare), 50 per cent; leukocytes, 29,600; neutrophilic polymorphonuclears, 14 per cent; metamyelocytes, 11 per cent; myelocytes, 4 per cent; large lymphocytes, 50 per cent; small lymphocytes, 6 per cent; myeloblasts, 2 per cent; monocytes, 2 per cent; normoblasts, 4 per hundred white cells; megaloblasts, 3 per hundred white cells.

The Wassermann and Kahn reactions of the blood were negative.

The patient declined progressively and died on November 15.

Autopsy, was made five hours after death and was complete with the exception of the skull. The anatomic diagnosis was carcinoma of the left breast with metastases to the left axillary nodes, liver, spleen, pleura, retroperitoneal nodes and marrow. A section of femur, removed from the site of a metastasis disclosed in the x-ray film, showed on gross examination the metastatic growth apparently situated in the red marrow, and it was noted that in some areas hyperplastic red marrow was replacing yellow marrow.

From the Pathology Laboratory of the New York City Cancer Institute, Division of Cancer, Department of Hospitals; Dr. Ira I. Kaplan, director.

1. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, Berlin, Julius Springer, 1931.

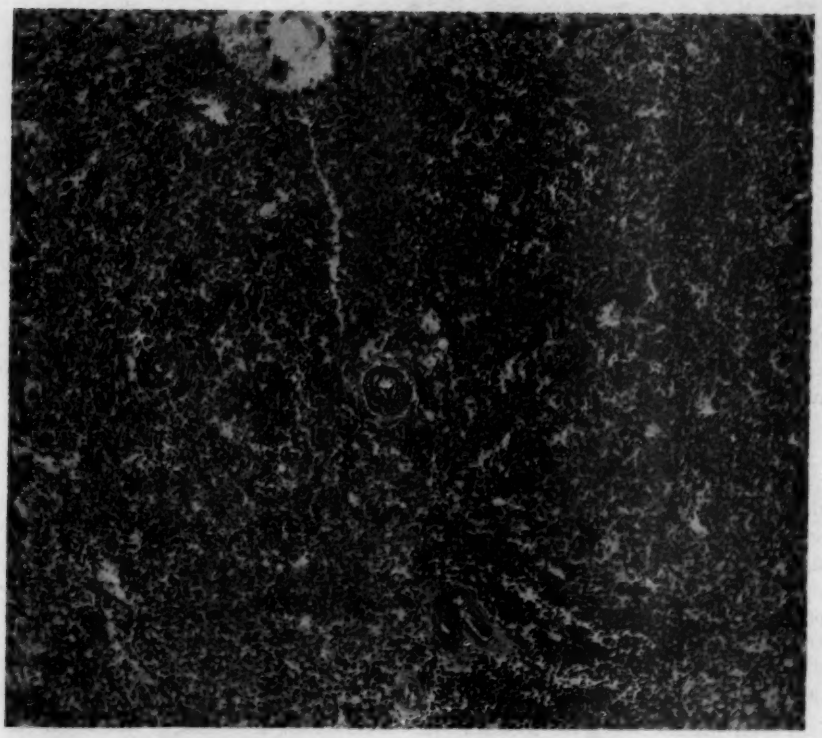

Fig. 1.—Areas of myeloid proliferation in the spleen, consisting of nests of hemocytoblasts, normoblasts, myeloblasts and myelocytes.

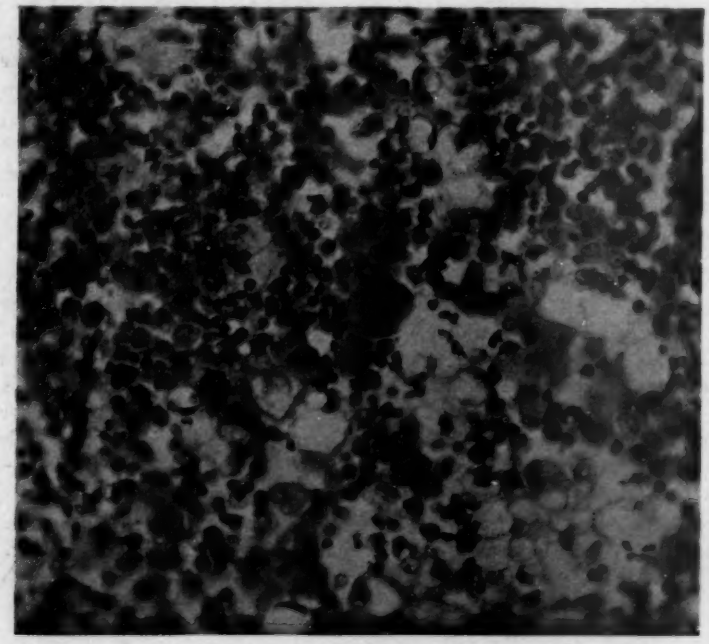

Fig. 2.—Hemopoietic foci in the liver. The cells here are mainly myeloblasts, megakaryocytes and normoblasts.

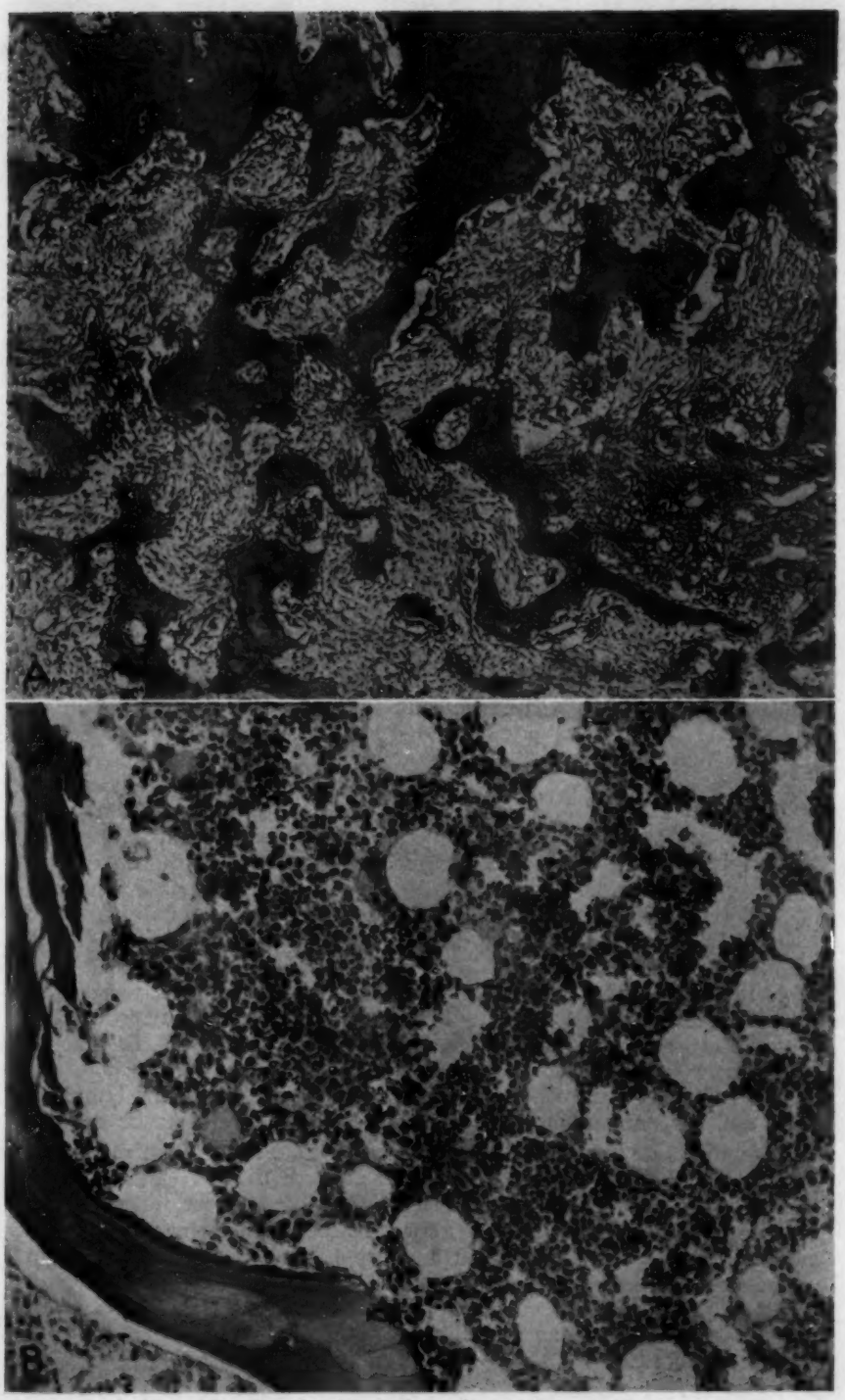

Fig. 3.—*A*, bone invaded by metastatic tumor cells. Adjacent to the spreading tumor cells are wide zones of proliferating connective tissue, resembling fibrous osteitis. *B*, hyperplastic red marrow replacing yellow marrow, consisting mainly of myeloblasts, promyelocytes, normoblasts and megakaryocytes, adjacent to the areas of fibrosis shown in *A*.

Histologic examination of the tumor of the breast disclosed a duct cell carcinoma, the structure of which was reproduced in all the metastases. The matter of arresting interest was the heterotopic hemopoiesis in the spleen and liver and the compensatory hemopoiesis in the yellow marrow. In the spleen, those areas which were not involved by metastatic growths showed hyperplasia of the so-called histiocytic reticulum. Here also were areas of myeloid proliferation, consisting of nests of hemocytoblasts, normoblasts, myeloblasts and myelocytes (fig. 1). In the liver, hemopoietic foci of the same type were seen, and the cells here were mainly myeloblasts, megakaryocytes and normoblasts (fig. 2). In the bones, the metastases extended into all the interstices. The bony trabeculae were surrounded, and the canals were invaded. Peripherally and adjacent to the spreading tumor cells there were wide zones of proliferating connective tissue resembling fibrous osteitis (fig. 3*A*). Immediately adjacent to these areas of fibrosis, instead of the yellow marrow usually present, there was hyperplastic red marrow, consisting mainly of myeloblasts, promyelocytes, normoblasts and megakaryocytes (fig. 3*B*).

COMMENT

A picture characterized by the presence of immature white cells of the myeloid and lymphoid series and immature red cells in the peripheral blood stream, associated with extensive visceral and skeletal carcinomatosis, has been well described by Vaughan and Turnbull.[2] Although one is under the impression that generalized carcinomatosis would eventually lead to an anaplastic state because of the destruction of hemopoietic marrow, as described by Frank,[3] it is difficult to accept this view here. The blood picture in this case is characterized not so much by its severity as by the number of immature white and red cells in the peripheral blood, cells which are normally confined to the marrow as precursors of leukocytes and erythrocytes. The cellular changes in the peripheral blood are therefore directly the opposite of those expected to follow death of the hemic components of bone marrow. At autopsy most of the marrow normally occupied by hemopoietic cells was found replaced by tumor. There was present, however, an extension of deep red marrow, microscopically free from adipose cells, into parts of long bones that are normally almost entirely adipose tissue. It is, to be sure, impossible to determine just how much active hemopoietic marrow there is in a skeleton containing scattered metastatic tumors, but the amount in this case seemed to exceed the normal, and there was, in addition, extremely active extramedullary hemopoiesis in such parts of lymphoid tissue and parenchymatous organs as were free from neoplastic growth.

Crowding out or destruction of the primordial blood elements of the marrow must be definitely excluded as a cause of this leuko-erythroblastic state because almost complete ivory-like osteosclerosis of the skeleton due to carcinomatosis may be accompanied by little or no anemia, while mixed osteoclastic and osteoplastic metastases of lesser extent may be associated with a blood picture of this type. Moreover, this leuko-erythroblastic condition is not dependent on the extent of bone marrow replacement. This is best demonstrated in multiple myeloma of bone.

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2. Vaughan, E. L., and Turnbull, H. M.: The Anemias, New York, Oxford University Press, 1934.

3. Frank, E.: Berl. med. Wchnschr. **52**:961 and 1062, 1915.

The blood picture present here cannot be ascribed to destruction or crowding out of hemopoietic marrow by tumor tissue. It is therefore probable, as Vaughan and Turnbull pointed out, that the cellular changes in the peripheral blood depend on a single fundamental cause, which is at present obscure. The finding of extramedullary hemopoiesis almost suggests that malignant neoplasms stimulate hemopoiesis or, more likely, that cancer brings about conditions that favor a myeloid reaction. At any rate, mere stimulation of hemopoiesis appears insufficient to explain the leuko-erythroblastic anemia. The very presence of immature red and white blood cells in the peripheral circulation strongly suggests that a regenerative process is attempting to counteract destruction of these cells. In this case there were widespread petechiae, and there was active phagocytosis of blood cells in lymph nodes, marrow, liver and spleen. Hemorrhagic areas were present also at the border of cancer areas. These findings point to the possibility that the neoplasm caused in some manner loss of red and white cells, directly or through hemorrhage. Another possible explanation of the presence of immature cells, including reticulocytes, in the blood stream may be found in some impediment to normal cell maturation. Malignant disease may deprive hemopoietic cells of necessary food elements.

One sees, therefore, that the cause of the appearance of immature leukocytes and erythrocytes in the peripheral blood in association with diffuse carcinomatosis remains unknown, and the many blood pictures described, simulating various dyscrasias, are for the present best included in the one big chapter of unexplained dyshemopoietic leuko-erythroblastic anemias that in many cases accompany generalized neoplastic disease.

Laboratory Methods and Technical Notes

MUSEUM MOUNTINGS AT MINIMUM COST

C. P. Larson, M.D., C.M., and E. J. Levin,* Fort Steilacoom, Wash.

This method of mounting specimens for museum purposes should be of interest to many hospitals in which it is desired to preserve interesting pathologic specimens but not possible to do so because of the prohibitive cost of some types of clock glass and museum jar mountings. The method described here is inexpensive and easy to execute, and the end-result is a mounted specimen which shows the pathologic lesion with maximum visibility and beauty. The entire cost of preparing and mounting a specimen, if materials the same as those described here are used, should not be over 60 cents.

DESCRIPTION OF METHOD

We shall describe the preparation of a specimen from the time it is removed from the body until a finished mounted product is obtained. As a fixative, we recommend Klotz solutions [1] because in our experience they preserve the natural colors better, with less bleaching, than any other fixative which we have used. However, Kaiserling or any of the routine fixatives may be used. Place the specimen in Klotz solution 1 and leave for from one to ten days, depending on the size of the specimen and the density of the tissue. If it is left in this solution too long, a bleaching effect will be noted. While in this solution, it should be

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* Technician.

From the Western State Hospital Pathology Laboratory.

1. The Klotz solutions are prepared as follows:

Stock solution no. 1

Sodium chloride	1,000 Gm.
Sodium bicarbonate	1,800 Gm.
Chloral hydrate	4,000 Gm.
Sodium sulfate	2,200 Gm.
Solution of formaldehyde U. S. P. (40 per cent)	6,000 cc.

Make up to 20,000 cc. with water. Mix 2,000 cc. of stock solution with 17,700 cc. of water and add 300 cc. of acetone.

Stock solution no. 2

Sodium chloride	1,000 Gm.
Sodium bicarbonate	1,800 Gm.
Sodium sulfate	2,200 Gm.
Chloral hydrate	2,000 Gm.
Solution of formaldehyde U. S. P. (40 per cent)	1,000 cc.

Make up to 20,000 cc. with water. Mix 2,000 cc. of stock solution with 17,900 cc. of water and add 100 cc. of acetone.

Directions: Keep two large crocks for each solution. Make up salts, solution of formaldehyde and water and allow to stand. Add the acetone when the batch is going to be used.

turned over occasionally during the first few hours and then inspected every twenty-four hours to note any change from the natural color. When properly handled, the tissue should become well fixed with no loss of natural color. Then place the specimen in Klotz solution 2 and leave for at least ten days before proceeding with the mounting. It is important to use a sufficient amount of the solutions to equal ten times the bulk of the specimen to be fixed. It is wise to ascertain the desired shape of the tissue before fixing, so that the tissue may be placed into the fixing solution in such a way as to retain this form. For example, in the case of a piece of the intestine, this may be laid out on a piece of white paper, to which it will adhere during the fixing, after which it will lay out flat with no support.

A standard clock or watch glass of the desired size (a diameter of 8 inches [20 cm.] will be suitable for most specimens) is then ground with emery powder so that the base will be perfectly smooth and hold a vacuum when apposed to the glass base plate. Grinding may be done on a large sheet of plate glass, using a coarse emery powder, such as grade 90, followed by a finer grade, such as emery flour. Grind by making a large sweeping circular motion of the clock glass

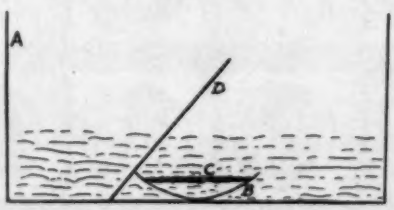

Fig. 1.—Drawing to show handling of base plate: *A*, pan; *B*, watch glass; *C*, specimen; *D*, glass base plate.

on the grinding plate. Wet the emery powder with water. A highly polished basal surface on the clock glass is the main essential, as it is to be held on the base plate by a vacuum. A suitable glass base plate is then selected, of a thickness depending on the diameter of the watch glass to be used. The reason for this is that, after sealing, the glass base plate assumes a concave shape, owing to the vacuum formed by the contracting fluid. If the base plate is too thick, it will not be able to give under the strain of the vacuum, and either it or the clock glass will crack. For the standard 5, 8 or 10 inch (12, 20 or 25 cm.) watch glass, a base plate with a thickness of ⅛ inch (0.32 cm.) is best. (Ordinary double strength window glass serves the purpose admirably.) The glass base plate should not have any scratches on the surface and should be cut 2 inches (5 cm.) wider than the diameter of the watch glass.

The fluid used for mounting (Klotz solution 2 or other desired solution) should be brought to a boil in the same pan that is used for mounting in order to get as much air as possible out of the fluid. Allow the fluid to cool to approximately 110 F. (44 C.). The mounting pan should be porcelain so that there will be no chemical reaction between the solution and the metals of the pan. It should be sufficiently wide and deep to allow for easy manipulation of the

specimen, clock glass and glass base plate. In placing these articles into the fluid, do so gently without causing any air bubbles. Put the specimen into the fluid and run the hands over it to get rid of air bubbles adhering to it. Then slide the clock glass under the specimen with the base upward and orient the specimen so that it fits in the concavity of the glass in the desired position. Place one of the square edges of the base plate on the bottom of the pan against the edge of the clock glass and gently lower the opposite edge of the base plate into the fluid so that any bubbles will rise up along the under surface of this glass (fig. 1). Bring the base plate into apposition with the whole under-surface of the clock glass, press firmly together, and lift the mount out of the fluid. Hold the mount up and inspect it for any air bubbles. In most cases the procedure described is sufficient to exclude all air from the mount, but if bubbles still

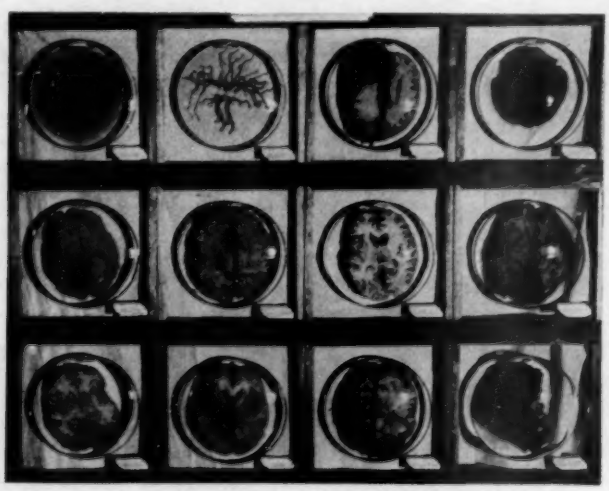

Fig. 2.—Mounts prepared by the method described.

remain in the mount, reimmerse it into the fluid with the clock glass down, and slide one edge of the base plate off the clock glass, allowing the air to escape. Then slide the base plate back into its proper position and remove the mount from the fluid. During the process of cooling, the mount must be placed flat on the table, or there will be a tendency for the clock glass to slide. If the base of the clock glass has been well ground, there will be no leaking of air into the mount. It is often necessary to clear the mount again, because air bubbles collect within, which have probably been sucked out of the tissue itself. The clearing is best done after the mount has been allowed to stand for a few days, at which time most of the air will have left the tissue and collected in the form of a single bubble. In order to clear this bubble, immerse the mount into the solution (heated to the same temperature in which the original mounting was done) and clear as already described.

The question arises as to how permanent and stable such a mount is under varying degrees of temperature. The clock glass will not drop off until the temperature in the surrounding air reaches a level higher than the temperature of the fluid in which the original mounting was done. The mount will also stand any temperature not lower than 45 F. (8 C.), but at a temperature lower than this there is danger that either the watch glass or the glass base plate will crack. The basic principle which makes this type of mount successful is that the glass base plate is thin enough to be able to accommodate to the contraction of the fluid by buckling inward, forming a concavity on the exposed surface.

No additional sealing is necessary, but a very thin rim of black cement placed around the edge of the watch glass will enhance the appearance of the mount. A very satisfactory and easy cement to apply is one developed by Muir and Judah, composed of Trinidad asphalt, linseed oil and oil of amber.[2]

To give the mount a finished appearance, we recommend a simple wood frame which fits around the edges of the base plate. Any type of picture framing is satisfactory, but there is one thing to be remembered in the framing, and that is, the frame must be loose to allow for the buckling of the base plate. Another method of obtaining a good appearance is to bevel the edges of the base plate by polishing with emery before mounting the specimen.

These mounts may be placed in a very inexpensive and attractive display rack, as shown in figure 2.

2. Muir, W., and Judah, E. L.: Internat. A. M. Museum Bull., 1915, no. 5.

SIMPLE SMALL PARAFFIN OVENS OR CONSTANT TEMPERATURE BATHS CONSTRUCTED AT SMALL COST

PAUL GROSS, M.D., PITTSBURGH

Electrically heated, thermostatically controlled small ovens find various applications in the laboratory. The pathologist may utilize such an oven in an automatic tissue-changing apparatus,[1] while the bacteriologist and the serologist may use such ovens for constant temperature baths. The apparatus is easily made and costs less than $3. The accuracy of three such baths which have been constructed has been better than ± 0.5 C. at 55 C.

CONSTRUCTION

In the construction, two "tin" cans, one fitting inside the other, are used. (The use of "tin" cans for paraffin ovens is permissible, but their use for water

From the Western Pennsylvania Hospital Institute of Pathology; Ralph R. Mellon, M.D., director.

1. Gross, Paul: A Hydraulic Automatic Tissue Changer or Immersion Device, Arch. Path. **23**:392, 1937.

baths is not recommended, because of the likelihood that they will rust. Copper is advised for the construction of these cans if the water is to be heated.) The inner can is 3¼ inches (8.26 cm.) in diameter and 5¼ inches (13.34 cm.) high. The outer can is 4 inches (10.16 cm.) in diameter and 5⅜ inches (13.65 cm.) high. The smaller can is closely and tightly wound with about 70 feet (21 meters) of no. 28 asbestos-covered nichrome wire,[2] beginning 1 inch (2.5 cm.) from the top and continuing to the very bottom. From the beginning and from the end of the winding a foot (about 33 cm.) of this wire should be allowed to protrude for connections. A bimetallic strip[3] ½ inch (1.27 cm.) wide and 12 inches (30.48 cm.) long is formed to fit snugly and evenly (at room temperature) about the outside of the inner can. Care must be taken to ascertain the direction in which the strip will bend when heated. The strip must then be

Fig. 1.—A photograph of the paraffin oven, showing the projecting binding post and bimetallic strip with the regulating screw.

formed so that the circle expands when the metal is heated. The overlapping portion of the strip is then bent almost radially at a point which leaves a gap of ¾ inch (1.91 cm.) in the circle (fig. 2).

A ¼ inch (0.64 cm.) hole is drilled in the center of the end which is to be fastened to the can. A similar hole is made near the top of the can at a point which leaves a ⅛ inch (0.32 cm.) margin between the bimetallic strip and the top of the can. The strip is then fastened to the can by means of the binding post indicated in figure 2. The latter is insulated from the container and the

2. This wire may be obtained from the Fisher Scientific Company, 709-719 Forbes Street, Pittsburgh.

3. Thermostatic bimetal strip (D-metal)—0.03 inch (0.07 cm.) thick, ½ inch (1.27 cm.) wide and 12 inches (30.48 cm.) long; cost, $1.25. This may be obtained from the Technical Service Bureau, Inc., 6805 North Clark Street, Chicago.

bimetallic strip by means of "shoulder fiber washers."[4] With the binding post and adjusting screw in position, the exact location of the contact point on the projecting end of the bimetallic strip is marked. The strip is then removed. A ¼ inch hole is drilled at this point and the contact screw fastened as in figure 2. The bimetallic strip is then permanently fastened to the can.

Connections are soldered as indicated in the diagram of the wiring (fig. 2). While soldering, care must be taken not to overheat the screw, lest the silver

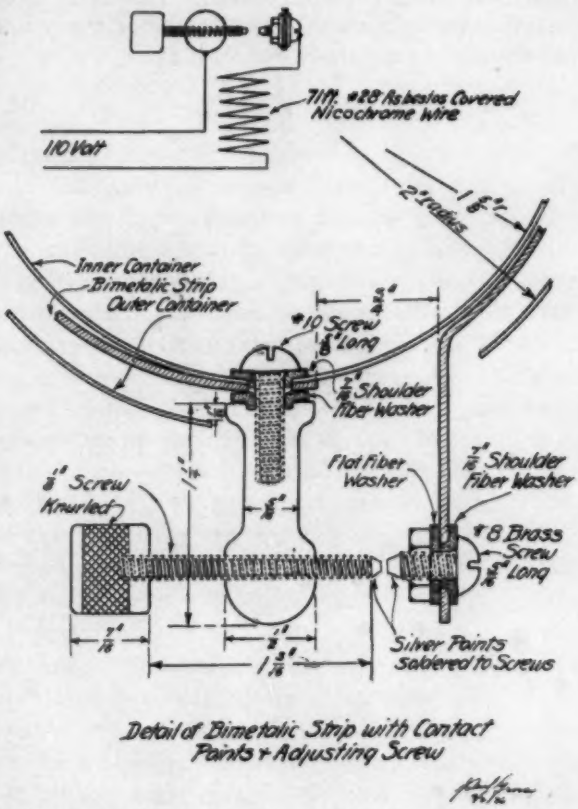

Fig. 2.—A diagram of the connections and a dimensional diagram of the temperature-regulating mechanism.

contact point become dislodged. The can is then wrapped with asbestos paper, leaving the bimetallic strip free. A slot is cut near the top of the outer can, 1½ inches (3.7 cm.) wide and 1 inch (2.5 cm.) deep, for the binding post and the projecting strip. (The outside container must not touch either.) Opposite this slot, near the base of the can, a hole is made to take a rubber grommet[5] for the electric

4. These are supplied by the Cameradio Company, 601-603 Grant Street, Pittsburgh, catalog no. 4307 A, type 94.

5. This can be obtained in any radio supply store or from the Cameradio Company.[4]

cord with plug. A disk of asbestos paper is inserted into the bottom of the outer container, and the inner can is placed on top of it. The open rims of the two cans are then soldered to a rim cut out of the top of the outer can.

The current consumption is about 42 watts.

SUMMARY

The details of the construction of an electrically heated, thermostatically controlled small oven are given. The oven is easily made. The current consumption is about 42 watts, the accuracy near ± 0.5 C. at 55 C., and the cost of materials less than $3.

General Review

RÔLE OF VITAMIN C IN RESISTANCE

DAVID PERLA, M.D.
AND
JESSIE MARMORSTON, M.D.
NEW YORK

INTRODUCTION

Though the importance of vitamin C in the maintenance of resistance to infection [1] has gathered support from numerous experimental and clinical observations in the past two decades, it is only in recent years that the problem has been approached systematically. In a recent review on the rôle of the adrenal glands in resistance, we emphasized that the mechanism of natural resistance is dependent on the maintenance of normal cellular metabolism and that procedures that impair the processes of oxidation and reduction depress the resistance of the somatic cells to all abnormal stimuli whether these are marked variations in temperatures or poisons, toxins or infectious agents. We further stressed that when the physiologic action of the adrenal cortical hormone is better understood, and when the chemical nature of the life-prolonging hormone of this gland is identified and the relation of the hormone to oxidation-reduction systems and cevitamic acid (introduced as ascorbic acid) is determined, a new approach to the problem of the mechanism of natural resistance in the body may be available.

The stimulus to this conception and to work in this field was greatly enhanced by the recent work on the close relationship between adrenal cortical function and cellular oxidation. In studying oxidation systems in plant life, Szent-Györgyi [2] succeeded in isolating hexuronic acid from cabbage and other plants. He found large amounts of this strongly reducing substance in the adrenal cortices of animals. In other tissues, it probably does not occur in comparable amounts. From its chemical properties this compound is apparently important in certain oxidation-reduction systems of cellular metabolism. Independently, Svirbely and

From the Laboratory Division of the Montefiore Hospital and the Laboratories of the Mount Sinai Hospital.

1. For recent reviews on the general subject of diet and resistance, see E. C. Robertson (Medicine **13**:123, 1934) and S. W. Clausen (Physiol. Rev. **14**:309, 1934).

2. Szent-Györgyi, A.: Biochem. J. **22**:1387, 1928.

Szent-Györgyi [3] and Waugh and King [4] identified hexuronic acid with the antiscorbutic vitamin C, and King isolated the same compound from orange and lemon juice concentrates.

This work opened a new field in the physiology of the adrenal cortex in relation to the utilization of vitamin C. Cevitamic acid is not identical with the life-prolonging hormone of the adrenal cortex, and more recent studies have failed to substantiate the theory that the adrenal cortex is essential to the production and physiologic activity of vitamin C. Nevertheless, there is probably a close interrelationship between the vitamin and the adrenal cortical hormone in their influence on certain anaerobic oxidation-reduction systems in cellular metabolism.

The availability of crystalline synthetic vitamin C offered an excellent opportunity for studying its relation to resistance and bodily functions. Its importance in the treatment of certain hemorrhagic diatheses has been suggested by Szent-Györgyi [5] and others. That an excess of vitamin C in the diet will appreciably raise the natural resistance of the organism is intimated by recent work in this field, but much remains to be established.[6]

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3. Svirbely, L. J., and Szent-Györgyi, A.: Biochem. J. **26**:865, 1932.

4. Waugh, W. A., and King, C. G.: Science **76**:630, 1932.

5. Szent-Györgyi, A.: Verhandl. d. Gesellsch. f. Verdauungs- u. Stoffwechselkr. **12**:49, 1934.

6. Recently St. Rusznyak and Szent-Györgyi (Nature, London **138**:27, 1936) described the isolation of a new vitamin factor (P) which is intimately associated with cevitamic acid. Previous work had led to the suggestion that cevitamic acid is accompanied in the cell by a substance of related activity and similar importance. In the absence of vitamin C, the symptoms of scurvy conceal the evidence of the deficiency of this factor. It was previously found that in certain pathologic conditions, such as the vascular type of hemorrhagic purpura, in which there are increased permeability and fragility of the capillary walls, cevitamic acid is ineffective. Such a condition can be readily cured, however, by the administration of extracts of Hungarian red pepper. These extracts are also effective in cases in which the capillary walls show permeability to protein only.

When fractioned, the active principle was found to be almost entirely flavonol. When used intravenously in the treatment of hemorrhagic purpura in amounts of 40 mg. a day, the spontaneous bleeding and evidence of capillary fragility ceased within two weeks.

The vitaminoid nature of the phenylbenzo-γ-pyrone dyes was demonstrated in a subsequent report by St. Rusznyak and Szent-Györgyi (ibid. **138**:798, 1936). A group of animals was given a scurvy-producing diet and another group the same diet plus 1 mg. daily of "citrin," the crystalline flavone fraction (vitamin P) of lemon juice. The animals receiving the scurvy-producing diet alone died in twenty-eight days with progressive loss in weight whereas the animals given this diet plus flavone lived, on an average, forty-four days. Both groups of animals showed signs of scurvy, with fragility of the bones, looseness of the teeth and swelling of the joints, but the number of hemorrhages in the flavone-fed animals was

(Footnote continued on next page)

II. EFFECT OF DEFICIENCY OF VITAMIN C ON THE FORMATION OF NATURAL ANTIBODIES

In a comprehensive study of the influence of deficient nutrition on the production of complement and amboceptor, Zilva [7] did not detect any difference in the content of natural antibodies in normal guinea-pigs fed an unrestricted mixed diet and those fed a scorbutic diet.

Koch and Smith [8] followed the variation in the titer of complement during the development and cure of scurvy in the guinea-pig. Twelve guinea-pigs were fed a diet of autoclaved soy bean meal, dried yeast, salt, cod liver oil and dried boiled cabbage. On this diet scurvy developed in from thirteen to sixteen days. The substitution of fresh cabbage for the dried boiled cabbage was sufficient to bring about normal growth. The titer of the complement was determined twice during the period prior to the dietary experiment, once during the height of scurvy and once after a period of starvation, when the animals had lost 20 per cent of their weight. The observers noted that during the period of scurvy the titer of the complement was appreciably increased and that during convalescence it fell but was slightly higher than normal. Starvation resulted in definite lowering of the titer. They suggested that there is an obscure connection between the complement of the serum and the natural effort of the body to compensate for the physiologic disturbance incident to scurvy. This hypothesis does not seem tenable.

Hamburger and Goldschmidt [9] observed no appreciable difference in titer of the complement between normal and scorbutic guinea-pigs or children. A slight increase in the complement of scorbutic subjects may be due to an increase in the protein content of the blood. The titers of the bacteriolysin and amboceptor of the serum of scorbutic animals were the same as those found for the normal animals. In testing for bacteriolysins, they employed Langer's method of mixing 0.1 cc. of serum with 0.5 cc. of a culture of Bacterium coli on cover

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strikingly less than the number in the other group. Vitamin P thus seems to have a marked and somewhat specific influence on the capillary system.

Experimental scurvy is apparently caused by the combined lack of vitamins C and P. Pure avitaminosis P presents no clinical symptoms, but the withholding of vitamin P in avitaminosis C will greatly modify this pathologic condition.

The authors, in a subsequent note (ibid. **139**:326, 1937), suggested that the therapeutic effects observed after administration of "citrin" in septic conditions and conditions accompanied by polyarthritis and endocarditis in man are partly due to its vitamin P content. The data on which this assertion is based have apparently not been published as yet.

7. Zilva, S. S.: Biochem. J. **13**:172, 1919.

8. Koch, M. L., and Smith, A. H.: Proc. Soc. Exper. Biol. & Med. **21**:366, 1924.

9. Hamburger, R., and Goldschmidt, L.: Jahrb. f. Kinderh. **100**:210, 1923.

slips in Petri dishes. After four hours' incubation of the culture, agar was poured into the dishes. The culture was then kept at 37 C. for twenty-four hours, and thereafter the colonies were counted. The use of Bact. coli was suggested because scorbutic infants frequently have pyelonephritis. Similar results were reported by Werkman, Nelson and Fulmer [10] from a study of the opsonic indexes of normal and scorbutic guinea-pigs to Bacterium typhosum and Staphylococcus albus.

Summary.—The natural antibodies are not depressed in scurvy, but complement may be increased.

III. EFFECT OF DEFICIENCY OF VITAMIN C ON THE FORMATION OF SPECIFIC ANTIBODIES

Scorbutic guinea-pigs showed no change in their capacity to form agglutinin against Bact. typhosum (Zilva [7]). Similar observations have been reported by Werkman, Nelson and Fulmer.[10]

Starvation and undernutrition disturbed the formation of antitoxin to diphtheria toxin in immature rats and guinea-pigs but had no effect on the development of immunity to Streptococcus erysipelatis in rabbits (Bieling [11]).

Bieling used 6 young rabbits, to 3 of which he gave a diet of oats, cloves and turnips, and to 3, only hay and a little clover. The animals were kept on these diets for about six weeks and were then given subcutaneous injections of increasing amounts (0.5, 0.7, 1, 1.5 and 2 cc.) of a culture of Str. erysipelatis. Seven days after the last injection, the immune body content of the serum was determined by means of protection tests, in mice. The tests were repeated two and three weeks later. The titer of immune bodies in the serum as thus determined was perhaps slightly higher for the starved than for the well fed rabbits.[11a] The differences were not statistically significant.

In subsequent studies Bieling observed that rats fed on a diet free from vitamin C did not produce antitoxin in sufficient concentration following injection of tetanus toxin to protect them against a dose of tetanus poison which the immunized well nourished rats all survived. Deficiency of vitamin C cannot be established in the rat, as this animal is capable of producing its own vitamin C. The depression in antitoxin was probably associated with deficiency in other dietary factors.[11b]

In another short experiment he fed guinea-pigs a scorbutic diet and on the fourth and ninth days after the onset of the experiment gave these animals, together with an equal number of controls, injections of formaldehydized tetanus toxin. Twenty-one days after the first immunizing injection, all the animals received a mixture of tetanus

10. Werkman, C. H.; Nelson, V. E., and Fulmer, E. I.: J. Infect. Dis. **34**: 447, 1924.

11. Bieling, R.: (*a*) Ztschr. f. Hyg. u. Infektionskr. **104**:631, 1925; (*b*) **104**: 518, 1925; (*c*) **106**:188, 1926.

toxin and antitoxin. Two of the scorbutic guinea-pigs presented tetanus, but none of the controls did. Similar tests were performed on scorbutic guinea-pigs with formaldehydized diphtheria toxin, administered subcutaneously at the same intervals. Controls (immunized normally fed guinea-pigs) which received injections of the toxin-antitoxin mixture twenty-one days after the first immunizing injection survived, but 4 of the 6 immunized scorbutic guinea-pigs died.

In unpublished experiments, we observed no depression in the hemolysin-forming capacity of rats fed for two months on a diet deficient only in vitamin C.

Summary.—Deficiency in vitamin C does not interfere with the formation of immune antibodies, although it does impair the effectiveness of immunization to tetanus or diphtheria toxin.

IV. EFFECT OF DEFICIENCY OF VITAMIN C ON SKIN SENSITIZATION AND ANAPHYLAXIS

Sensitivity to Diphtheria Toxin.—Alterations in the inflammatory response of the skin to diphtheria toxin have been observed in scorbutic guinea-pigs. Arkwright and Zilva,[12] however, who observed diminution in intracutaneous reactions to diphtheria toxin, attributed this to loss in weight on the part of the animals and not specifically to scurvy.

Guinea-pigs fed a diet of water and bran and very little cabbage gave much smaller reactions to injected fractions of the minimal lethal dose of diphtheria toxin than normally fed animals. Animals that grew fairly well gave prominent reactions, but those that lost weight gave slight ones. This effect was the same whether the decrease in weight was due to diminished intake of a normal diet or to a diet deficient in vitamin C. If the animals lost more than 50 Gm. in from five to six days, the inflammatory reaction was less than half the size observed in the animals of fair growth, and the cellular exudate in the local lesion was less pronounced.

Bieling[11b] observed increased sensitivity of scorbutic guinea-pigs to diphtheria toxin, although the local skin reactions to intracutaneous or subcutaneous injections were definitely less than those in normally fed guinea-pigs.

The guinea-pigs were fed a diet of autoclaved milk and oats for seventeen days to produce a scorbutic state. The intracutaneous tests were made with various dilutions of diphtheria toxin and subsequently with toxin-antitoxin mixtures. In control experiments, he fed animals a diet of fresh turnips in small amounts, fresh hay and water, which he considered an adequate normal diet, and found after a period of nine days that animals that had lost weight on small amounts of this normal diet showed slightly less edema about the areas of injection but a skin reactivity that was otherwise the same as in the normal animals.

12. Arkwright, J. A., and Zilva, S. S.: J. Path. & Bact. **27**:346, 1924.

Bieling's experiments were performed on very small numbers of animals. The diet certainly was deficient in more than vitamin C. We believe that this criticism applies to many of the reports in this field, for it has been assumed that if the diet produced scurvy in the guinea-pig no essential factor other than vitamin C was absent. In most instances, unless special precautions were taken, the diet, while it was scurvy-producing, was really free from all vitamins.

Sensitivity to Tuberculin.—Similarly, the skin reactions to intracutaneous injections of tuberculin in scorbutic tuberculous animals are definitely diminished as compared with those in normally fed tuberculous animals (Bieling[11b]). Underfed animals demonstrate a similar depression in skin reactivity. Though this indicates that the vascular reaction is diminished in hunger, it is not an index of the effect of the bacterial poison on any other tissue cells of the body. Bieling injected tubercle bacilli into 10 guinea-pigs, and ten weeks later placed some of these animals on a scorbutic diet and some on normal fodder. When he then injected tuberculin subcutaneously, the animals fed a scorbutic diet during a period of a few days succumbed more readily than the controls.

The observation that scorbutic tuberculous guinea-pigs react less to intracutaneous injections of tuberculin and show diminished skin reactions as compared with nonscorbutic tuberculous animals was confirmed by Prausnitz and Schilf.[13]

Sensitivity to Drugs.—Frei[14] reported that he was able to sensitize the skin of guinea-pigs to neoarsphenamine, but that animals on summer fodder were more resistant than those on winter fodder. The experiments with paraphenylendiamine showed a similar variation in resistance. Sulzberger and Oser[15] attributed this to a varying content of vitamin C in the diet.

They fed animals a basic diet of dried autoclaved milk, oat flakes, the whites of eggs, cod liver oil and dried hay. They had observed that animals fed such a diet lost weight after from ten to fifteen days, showed clinical signs of scurvy and died in from three to four weeks. After a period of ten days on this basic diet the animals in the experiment under consideration were divided into five groups. To the diets of the different groups cevitamic acid was added in amounts varying from 0.25 to 2 mg. Ten days later all the animals were given intracutaneous injections of a 0.15 per cent solution of neoarsphenamine in saline solution—0.1 cc. to each. None of the animals showed an immediate reaction, but some showed a flare up from six to ten days later. On the twenty-eighth day, or eighteen days after the first injection, each animal was given a second injection of neoarsphenamine in the opposite flank. Within twenty-four hours the sensitized animals showed a severe local reaction that progressed in severity.

13. Prausnitz, C., and Schilf, F.: Deutsche med. Wchnschr. **50**:102, 1924.

14. Frei, W.: Klin. Wchnschr. **7**:1026, 1928.

15. Sulzberger, M. B., and Oser, B. L.: Proc. Soc. Exper. Biol. & Med. **32**: 716, 1934.

Hypersensitivity was evident in most of the guinea-pigs that received 1.5 mg. or less of cevitamic acid per day as a supplement to their diet. Scurvy, however, occurred only in animals that received 0.5 mg. or less of cevitamic acid per day. Of 9 animals given 2 mg., 6 showed no reaction. An occasional cachectic animal among those that received the smallest amounts of cevitamic acid failed to react.

This experiment is extremely interesting and was well controlled. According to Chapman and Morrell,[16] however, when animals were fed on a diet of a grain mixture and carrots, no sensitization to neoarsphenamine could be achieved. If 2 mg. of cevitamic acid was added to the diet of each, daily severe reactions were obtained with the sensitizing and the provocative doses. It is hard to reconcile these divergent findings, though the conditions of the experiments of Chapman and Morrell did not duplicate in detail those of Sulzberger and Oser.[15]

Sensitivity to Poison Ivy.—Recently Simon observed that a dietary deficiency in vitamin C inhibited the development of hypersensitiveness to poison ivy in guinea-pigs.[17]

He divided 24 guinea-pigs into six groups of 4 animals each. Four of the groups received diets deficient, respectively, in vitamin A, vitamin B, vitamin C and vitamin D; two groups were given a full diet.[18] Sixteen days after the onset of the experiment, 5 animals in the first four groups were dead. At this time, each of the surviving animals in the first five groups was given a cutaneous application of an extract of poison ivy.[19] Ten days later, all the animals were tested by cutaneous applications of the extract in dilutions of 1:10, 1:40 and 1:100. Readings made on the following day showed well developed sensitivity in all the prepared groups except those given a diet deficient in vitamin C. No other dietary deficiency influenced the result.

Anaphylaxis.—As early as 1911, Lesne and Dreyfus[20] observed that starvation in rabbits diminishes their response to anaphylaxis. Rabbits were given injections of egg white intravenously and for fifteen days thereafter were fed a normal diet. Four days prior to the administration of the shocking dose, the animals were placed on a diet exclusively of water. The period of starvation tended to suppress the anaphylactic

16. Chapman, C. W., and Morrell, C. A.: Proc. Soc. Exper. Biol. & Med. **32**:813, 1935.

17. Simon, F. A.: J. Immunol. **30**:275, 1936.

18. The diet deficient in vitamin A consisted of casein, corn starch, dried brewers' yeast, salt mixture, autoclaved alfalfa and distilled water. The diet deficient in vitamin B contained casein, corn starch, butter fat, autoclaved yeast, cod liver oil, salt mixture, alfalfa and water. The diet deficient in vitamin C consisted of ground whole oats, heated skim milk powder, butter fat, table salt, autoclaved alfalfa and distilled water. The one deficient in vitamin D consisted of ground yellow corn, ground wheat, wheat gluten, gelatin, calcium carbonate, sodium chloride and distilled water. The full diet contained hay, oats, carrots, lettuce, cabbage and water.

19. A 10 per cent acetone extract of Rhus toxicodendron radicans.

20. Lesne, E., and Dreyfus, L.: Compt. rend. Soc. de biol. **71**:153, 1911.

reaction. Similar results were observed by Konstansoff [21] in guinea-pigs sensitized to horse serum, egg white or cow's milk. According to Pierret and Crampton,[22] starvation of as short a period as thirty-six hours prevented anaphylactic shock in guinea-pigs sensitized subcutaneously to horse serum if the period of starvation immediately preceded the injection of the shocking dose. Zolog [23] could not confirm this observation, but in a carefully controlled series of experiments he noted that guinea-pigs fed a diet deficient in vitamin C prior to sensitization were less sensitive to the reinjected antigen than the controls.

The basic diet was dried grass and oats. The controls received fresh grass and beet root in addition. The guinea-pigs were fed the diet for thirty days prior to the first injection of the antigen—horse serum in some of the experiments, and in others, red cells of the horse. Fifteen days after sensitization, they were given reinjections of the antigens and those that had received the scurvy-producing diet survived greater shocking doses than the controls. They survived five times the control amount of red blood cells, and in one experiment, ten times the control amount of horse serum.

Zolog controlled the factor of inanition by duplicating the conditions of experiments of Pierret and Crampton [22] but observed no depression in reaction in animals starved for a short period prior to the injection of the shocking dose. He concluded that the hyposensitivity to anaphylaxis is greater the longer the period during which the guinea-pig is on the scurvy-producing diet and the younger the animal.

It is interesting, however, that the interval of time during which the animals are fed the scurvy-producing diet is important in determining the variations in sensitivity. Sartori,[24] for example, observed that if guinea-pigs are fed on a diet deficient in vitamin C for a period of five days prior to the injection of the sensitizing dose they are more sensitive to anaphylactic shock than are normally fed animals. If, however, the vitamin-deficient diet is instituted after sensitization has occurred, no effect is observed on the subsequently induced anaphylaxis. The avitaminosis in guinea-pigs may shorten the period of anaphylactic incubation to as little as five days instead of a normal period of fifteen days. However, at the end of thirty-three days, the animals are still as sensitive as in the early periods. This work was confirmed by the experiments of Sereni,[25] who fed his guinea-pigs a scurvy-producing diet of bread, oats and milk for thirteen days prior to sensitization. As early as the eleventh day the animals with scurvy were killed by a second injection, but normally fed animals tested on the same day

21. Konstansoff, S.: Compt. rend. Soc. de biol. **72**:263, 1912.
22. Pierret, A., and Crampton, C. W.: Compt. rend. Soc. de biol. **89**:1282, 1923.
23. Zolog, M.: Compt. rend. Soc. de biol. **91**:215, 1924.
24. Sartori, C.: Pathologica **17**:160, 1925.
25. Sereni, E.: Boll. d. Soc. ital. di biol. sper. **2**:254, 1927.

survived. When tested on the twentieth day with the same shocking doses, both scorbutic and normal animals succumbed. He attributed this discrepancy to the fact that animals with scurvy produce antibodies at a slower rate than do normal animals. He did not, however, offer any proof of this assumption. Guinea-pigs fed for some time on a scurvy-producing diet and passively sensitized survived an intracardiac injection of serum administered twenty-four hours later. The guinea-pigs fed a normal diet and similarly treated succumbed. He concluded, however, that the scorbutic animals were more sensitive than the controls to anaphylaxis.

Hurwitz and Wessels [26] observed that guinea-pigs fed for four weeks on a diet of rolled oats, milk and bran and then sensitized with horse serum showed a modification in the response of the sensitized uteri examined in vitro three weeks later, but not in the response of the bronchi.

The uterine segments were suspended in Locke's solution, and the bronchial muscle reaction was studied by bronchial perfusion of the sensitized lungs. The uterine muscle strips from those animals that had been fed the scurvy-producing diet failed to respond either to antigen or to smooth muscle stimulants. The introduction of the same substance into the bronchi (histamine, posterior pituitary, barium or horse serum) caused bronchial constriction in both the vitamin-deficient and the normally fed animals.

Summary.—In animals deficient in vitamin C there is a decrease in sensitivity of the skin, as indicated by diminished reactions to injections of diphtheria toxin and to injections of tuberculin. This diminution in skin sensitivity is, however, associated with greater susceptibility of the animals to the toxic effects of parenteral injections of these poisons. Skin reactivity to drugs, such as arsphenamine, may be elicited in guinea-pigs previously treated by injections of small amounts of such drugs if these animals are fed a diet deficient in vitamin C but not completely depleted of this factor. In animals whose avitaminosis is sufficient to cause clinical manifestation of scurvy the skin is no longer reactive.

This is also true of skin hypersensitiveness to poison ivy. A short period of vitamin C deficiency prior to the administration of the sensitizing dose of protein antigenic substances increases the anaphylactic response to the subsequent injection of the shocking dose and shortens the period of incubation of anaphylactic sensitization. Extreme scurvy or periods of starvation may under certain conditions impair the anaphylactic response. There is diminution in the smooth muscle response of the uterus in the scorbutic sensitized animal to smooth muscle stimulants and antigen.

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26. Hurwitz, S. H., and Wessels, A. L.: Proc. Soc. Exper. Biol. & Med. **29**:122, 1931.

In general, subclinical scurvy may be associated with increased sensitivity of the skin to poisons and tuberculin and increased susceptibility of the body to anaphylaxis, but frank scurvy may be accompanied by suppression of the skin reaction and depression of the general susceptibility to anaphylaxis.

V. EFFECT OF DEFICIENCY OF VITAMIN C ON NATURAL RESISTANCE TO POISONS AND TOXINS

Vercellana [27] observed that guinea-pigs deficient in vitamins were less resistant to a number of drugs and poisons than were normally fed animals.

> The animals did not survive injections of barium carbonate, atropine, alcohol, spartein, nicotine, quinine, epinephrine and the toxin of Bacterium dysenteriae (Shiga) in amounts that were readily tolerated by normal animals. Scorbutic guinea-pigs were killed by an amount of strychnine nitrate equal to a third of the minimal lethal dose for normal guinea-pigs. In part, this was due to undernutrition, as animals starved for two or three days prior to the injection of the drug also showed a drop in resistance, but to a lesser degree than that observed in the vitamin-deficient group. Similarly, the minimal lethal dose of a fungus poison (aqueous extract of Russula nigrigans) administered subcutaneously to scorbutic guinea-pigs was reduced to less than a sixth of the corresponding dose for normally fed guinea-pigs. The normal animals were killed by 4 cc. of a concentrated fungus solution; the vitamin-deficient animals, by less than 1 cc. Animals starved for two or three days also died following the injection of 1 cc. of the fungus solution.

Here, obviously, the drop in natural resistance was largely a matter of general undernutrition.

Latent scurvy in infants is associated with a relatively high incidence of nasal diphtheria, according to Hess.[28] This drop in local resistance occurs even though the blood of the infants contains sufficient antitoxin to afford protection; negative Schick tests were obtained in spite of clinical diphtheria. Hess [28] explained this apparent paradox by stating that the lack of antiscorbutic vitamin exerts a local effect on the mucous membrane which diminishes its immunity, but at the same time does not act to lower systemic immunity.

Significant of the effect of a dietary deficiency of vitamin C on resistance to a bacterial toxin are the results of the carefully controlled studies of King and Menten.[29] They found that there is a wide zone of vitamin C deficiency without the appearance of frank scurvy in which

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27. Vercellana, G.: Ann. d'ig. **38**:364, 1928.

28. Hess, A. F.: Scurvy: Past and Present, Philadelphia, J. B. Lippincott Company, 1920.

29. King, C. G., and Menten, M. L.: J. Nutrition **10**:129, 1935.

the physical processes are subnormal and the animal is more sensitive to injury from bacterial toxin.

In their studies, the diphtheria toxin was diluted in sterile saline solution and administered subcutaneously. Determinations of tissue respiration were made on 100 mg. of liver and kidney suspended in Locke's solution, by means of the Barcroft-Warburg constant volume manometric apparatus. The oxygen consumption from air was recorded at thirty minute intervals over a period of two hours. Determinations of vitamin C were made on the tissues by a titration method using trichloro-acetic acid and 2-6 dichlorophenolindophenol. They observed that single injections of amounts of diphtheria toxin containing 1.5 or 2 M. L. D. produced extensive lesions. The survival time of 5 animals receiving 5 mg. of pure vitamin C daily prior to the injection of the toxin was greater than that of 4 animals depleted of vitamin C until mild indications of scurvy were present. With smaller repeated doses of toxin (0.1, 0.3 and 0.5 M. L. D.) the differences were more striking. The injection of toxin into normal guinea-pigs produced degeneration and hemorrhage of the adrenal cortex. Similar effects occurred as a result of vitamin C deficiency alone. The vitamin C content of the tissues was unaltered in animals given injections of the toxin. Guinea-pigs receiving vitamin C daily—some at an abundant, protective level (0.5 mg. cevitamic acid) and some at a subprotective level (0.25 mg.)—were given subcutaneous injections of standardized diphtheria toxin in amounts of 0.1, 0.3, 0.5 and 1 M. L. D. In animals in which the reserves of vitamin C were partially depleted without their showing external signs of scurvy the time of survival following the injection of lethal amounts of toxin was shortened about 50 per cent and the loss in weight was more severe. Hemorrhage and necrosis at the sites of injection were more marked in the animals suffering with latent scurvy. The decrease in the oxygen consumption of the hepatic and renal tissue after injection of the toxin was in the range of from 5 to 15 per cent.

These studies indicate that latent scurvy in guinea-pigs is associated with increased sensitivity to a bacterial toxin parenterally administered.

In subsequent studies, Menten and King [30] observed the production of diffuse hyperplastic arteriosclerosis and degeneration in various tissues in guinea-pigs maintained on diets deficient in vitamin C and given injections of sublethal amounts of diphtheria toxin. Such animals also had hydropic degeneration of the islets of Langerhans, associated with hyperglycemia and low tolerance to sugar. With recovery, the pancreatic lesions disappeared.

In the medium-sized arterioles of the liver, lung, spleen and kidney were found connective tissue proliferation of the media and swelling of the internal elastic lamella, with degenerative changes in the smaller vessels. The smooth muscle showed marked swelling, pyknosis and necrosis. This was associated with loss of resiliency and tone in the elastic fibers, induced by compensatory hyperplasia of the connective tissue of the arteries. In larger vessels the changes began in the media, with gradual complete involvement and thinning of the vessels. No

30. Menten, M. L., and King, C. G.: J. Nutrition **10**:141, 1935.

compensatory fibrosis was found, but nodules of cartilage such as are seen in old guinea-pigs occurred.

In guinea-pigs each of which was given 0.25 mg. of cevitamic acid daily and 0.1 M.L.D. of diphtheria toxin on the fourteenth, seventeenth, twenty-first and twenty-fifth days, no such changes occurred. However, diffuse hyperplastic arteriosclerosis was produced with 0.3 M.L.D. regardless of the level of the vitamin C in the diet. This condition cannot be produced in such animals as the rat, which synthesizes its own vitamin C. The vitamin C content of smooth muscle is comparatively low, and it can readily be reduced in amount. Degenerative lesions of the islets of Langerhans can readily be produced with other organisms, such as Bacterium enteritidis (Gaertner). The lesions are restricted to the beta cells, the nuclei of which show vacuolation and pyknosis. The same amount of toxin is required to produce lesions of the islets as to produce vascular lesions in the presence of relative vitamin C deficiency.

Wolbach and Howe [31] showed that in the guinea-pig an adequate intake of vitamin C is indispensable for the formation and the integrity of collagen. Menten and King [30] suggested that the metabolism and respiration of connective tissue intimately adjusted to such relationship, and that perhaps this accounts for the unique vascular response to a variety of infectious agents injected into guinea-pigs with latent scurvy.

Summary.—Latent scurvy in animals and man is associated with marked increase in their susceptibility to drugs and bacterial toxins. The vascular injury produced by the toxins of certain bacteria, such as Corynebacterium diphtheriae, is more pronounced in the presence of deficiency of cevitamic acid. Such injury is associated with decrease in tissue respiration.

VI. EFFECT OF DEFICIENCY OF VITAMIN C ON NATURAL RESISTANCE TO SPONTANEOUS INFECTIONS

Observations of spontaneous infections in experimental animals with latent or manifest scurvy are scattered. Theobald Smith [32] noted in guinea-pigs epizootics of dysentery and of pneumococcic pneumonia and pleurisy that occurred at the times of the year when green food was given in minimal amounts. Such epizootics have been interpreted by others as due to latent scurvy in the guinea-pigs.

Guinea-pigs fed a diet of crushed oats and autoclaved milk, which is deficient in vitamin C, show severe changes in the gastro-intestinal tract, such as congestion, hemorrhage, ecchymoses, punched-out ulcers, particularly of the duodenum, and thinning of the walls of the large

31. Wolbach, S. B., and Howe, P. R.: Arch. Path. **1**:1, 1926.
32. Smith, T.: J. M. Research **29**:291, 1913.

intestine. Degenerative changes are found in the myenteric plexus, and necrotic changes, in the cellular elements of the mucous membranes. These changes in the intestines, McCarrison [33] pointed out, often occur before other signs of scurvy are manifest and permit bacterial invasion to occur.

Höjer [34] maintained that guinea-pigs fed a diet deficient in vitamin C readily contract infections. Of 189 animals with scurvy, 60 suffered from acute infections, mainly of the upper respiratory tract, and from pneumonia, septicemia and enterocolitis. Animals with latent scurvy showed about twice as many infections leading to death as those on a complete dietary. Of 72 animals fed an insufficient antiscorbutic diet, 47 per cent showed signs of infection as compared with 20 per cent of the controls. Of 62 animals fed an absolutely scorbutic diet, 29 per cent showed signs of acute infections. However, the life span was twice as long in guinea-pigs fed a relatively deficient antiscorbutic diet as in those fed an absolutely scorbutic diet.

Clinical observations on the association of latent and manifest scurvy with infections are numerous. Hess [35] stated that the scorbutic state even in the absence of frank symptoms of scurvy lowers the resistance of the subject to such infections as diphtheria.

During the World War, latent and manifest scurvy occurred among the soldiers of the Turkish and Russian armies. Coincident with the appearance of scorbutic manifestations there was apparent increase in acute infections. Typhoid fever in patients with scurvy ran a severe course. The high incidence of dysentery and malaria was in part attributed to the undernutrition of the soldiers. Latent scurvy became manifest scurvy with the onset of infection. In general, there was noticeable increase in the hemorrhagic character of the exanthems, which Salle and Rosenberg [36] and others attributed to concomitant latent scurvy. Patients with tuberculosis who acquired scurvy readily succumbed. Tuberculosis in persons with latent scurvy was rapidly fatal. The incidence of tuberculosis among the undernourished Turkish soldiers was considerable. An attempt to arrive at an accurate analysis of the factors underlying the statistics on the incidence of infections during and after the war and their relationship to undernutrition is hazardous. There is little doubt that infectious diseases increased among soldiers exposed to the conditions of crowding, herding, poor sanitation and undernutrition. The civilian population as well suffered from infections in increasing numbers. The new generation showed

33. McCarrison, R.: Indian J. M. Research **7**:167, 1919.

34. Höjer, J. A.: Acta pædiat. (supp.) **3**:8, 1924.

35. Hess, A. F.: New England J. Med. **207**:637, 1932.

36. Salle, V., and Rosenberg, M.: Ergebn. d. inn. Med. u. Kinderh. **19**:31, 1921.

increased susceptibility to many infections, such as tuberculosis, for many years after the war. But it is impossible to attribute this to the deficiency in any one dietary factor, though it is readily conceded that undernutrition contributed greatly to the depression in natural resistance.

Rosenbund [37] observed that the diminished resistance to infection in infants with scurvy, as determined by the high incidence of transient infections, is not rapidly altered by curing the scurvy. For several months after antiscorbutic treatment is administered, intercurrent infections are as frequent as in the scorbutic state. Infants with latent scurvy not only are subject to more frequent infection but may present manifest scurvy following a minor infection, such as vaccination against smallpox. Stern [38] observed in a series of 23 infants with latent scurvy severe reactions following injections of cowpox lymph. Fever developed, with hemorrhages at the sites of vaccination.

Patients with scurvy who die generally present at autopsy evidences of severe infection. Schagen [39] reported that in half the autopsies on a series of scorbutic children active tuberculosis was observed. Pneumonia, grip, otitis, furunculosis and pyuria are common in scorbutic children (Reyher [40]). Similar observations were reported by Dubois,[41] who noted the frequency of infections of the upper respiratory and of the urinary tracts. The administration of vitamins, particularly vitamin C, was followed by the disappearance of many of the infections.

Höjer [34] discussed at length the relation of scurvy to tuberculosis. Tuberculosis may influence latent scurvy in many ways. The diminished appetite may lead to insufficient consumption of vitamin C. The intestinal tract may change so that the consumed dose is not absorbed. Scorbutic atrophy of the vascular wall may be associated with hemorrhage in the region of the tuberculous focus. The resistance of the body to tuberculosis is lessened during the course of scurvy in patients, as is evidenced by numerous observations. In the northern provinces of Sweden, fresh vegetables are as rare as tuberculosis is frequent (Höjer). Höjer's observations led him to suggest that vitamin C in fully protective amounts should be given to persons suffering with tuberculosis, particularly children. His observations on the therapeutic value of vitamins in a part of Sweden where fresh vegetables are scarce suggested the importance, apparently, of adequate vitamin C in the diet of tuberculous patients. These therapeutic tests were made in 70 selected cases of tuberculosis of equal severity; half of the patients were given

37. Rosenbund, R.: Ztschr. f. Kinderh. **34**:333, 1922.
38. Stern, R.: Ztschr. f. Kinderh. **36**:32, 1923.
39. Schagen, B.: Jahrb. f. Kinderh. **104**:225, 1924.
40. Reyher, P.: Arch. f. Kinderh. **76**:215, 1925.
41. Dubois, R.: Nourrisson **19**:337, 1931.

orange juice as a dietary supplement. Höjer [34] believed that the patients treated with orange juice improved.

The frequent association of scurvy and spontaneous infection led to the erroneous conclusion that scurvy was due to an infection, and, as late as the war, "organisms" were isolated from the tissues of scorbutic animals that were held responsible in part for the changes observed in scurvy. The endemic occurrence of scurvy, the presence of acute infections in association with the onset of the disease in the subjects and the frequent occurrence of scurvy with fever suggested the dependence of scurvy on infection. Though in man scurvy frequently becomes manifest in association with infection, in guinea-pigs, in a high percentage, infection does not accompany scurvy. When infection occurs it is merely a concomitant manifestation due to the lowered resistance of the host with latent or manifest scurvy. In animals the infections that appear spontaneously do so as a rule late in the disease. There is little doubt that in animals and man the scorbutic state is associated with increased susceptibility to spontaneous infection. What part is due solely to a deficiency specifically of vitamin C, what part to general undernutrition and what part to concomitant deficiencies of other dietary factors is not well established.

In this connection, the studies of Finkle [42] are of interest. He reconsidered the question of the rôle of vitamin C deficiency in the etiology of pathologic conditions other than scurvy. Using the method of Harris, Ray and Ward,[43] he confirmed their observations that in normal persons from 0.03 to 0.05 mg. of cevitamic acid was excreted per cubic centimeter of urine during the day.[42a] He studied the excretion of vitamin C before and after intravenous administration of 100 mg. of cevitamic acid to each of 127 patients suffering from a variety of conditions and to a number of normal controls. He observed that in about from two to three hours after the intravenous administration of vitamin C the cevitamic acid excreted in the urine rises to levels from five to six times as high as the preinjection levels. In cases in which the preinjection output of vitamin C in the urine fell much below 0.03 mg., the total output for the twenty-four hour period was considerably below the normal level. In these cases, the intravenous administration of vitamin C was not followed by a rise in the vitamin C excreted in the urine during the twenty-four hour period.

The excretion and utilization of vitamin C were studied by this method in the following conditions: purpura haemorrhagica, hemophilia,

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42. Finkle, P.: (*a*) Proc. Soc. Exper. Biol. & Med. **32**:1163, 1934; (*b*) Vitamin C Saturation Levels in the Body in Normal and in Various Pathological Conditions, to be published.

43. Harris, L. J.; Ray, S. N., and Ward, A.: Biochem. J. **27**:2011, 1933.

acute lupus erythematosus, acute glomerulonephritis, hypertension, acute rheumatic fever, rheumatoid arthritis, jaundice due to various conditions, Addison's disease (a few instances) and ulcerative colitis. He observed that of 14 patients with rheumatic fever, 5 showed a considerable increase in the excretion of vitamin C following the injection of cevitamic acid, even some whose preinjection level was lower than normal. However, most of the patients in this group showed a daily excretion of vitamin C below the normal level.[44] Two patients showed an excretion above this level.

Of 24 patients with rheumatoid arthritis, only 4 showed a normal curve of excretion of vitamin C in the urine. The remaining ones either had excretion levels below the normal or no rise following intravenous administration of cevitamic acid. He also observed a consistent disturbance in the metabolism of vitamin C in lupus erythematosus. In the 5 cases studied the excretion level was low even with adequate intakes of orange juice and did not respond to intravenous injections of vitamin C.

From his studies Finkle [42] concluded that a large percentage of a hospital population have an excretion of vitamin C below that of normal persons and suffer from varying degrees of subclinical scurvy, for the intravenous injection of vitamin C results in little or no rise in the cevitamic acid excreted in the urine. This degree of subclinical scurvy accompanies a variety of pathologic conditions. Finkle does not believe that deficiency of vitamin C has any causal relationship to any condition other than scurvy.

He is unable to explain, however, the disturbed metabolism of vitamin C that accompanies lupus erythematosus and rheumatoid arthritis.

VIII. EFFECT OF DEFICIENCY OF VITAMIN C ON NATURAL RESISTANCE TO EXPERIMENTALLY INDUCED INFECTIONS

Acute Infections with Staphylococcus.—Jaffe [45] made the interesting observation that guinea-pigs fed on a scurvy-producing diet and acquiring acute suppurative osteomyelitis did not manifest the cardinal symptoms of scurvy.

> Twelve guinea-pigs were fed a diet free from vitamin C. Scurvy developed in all of them in from thirteen to eighteen days. The wrists became tender and swollen; the teeth became loose; scorbutic changes occurred at the costochrondal junctions; there was cessation of the formation of new marrow, with diminution in the number of osteoblasts in the zone of calcification; rarefaction

44. Since marked increases in output followed injection of ascorbic acid, the author believes there is no disturbance of vitamin C metabolism in these cases.

45. Jaffe, H. L.: J. Infect. Dis. **40**:502, 1927.

of the existing cortex and irregularities of the spongy portion occurred; there were absorption of cartilage columns and formation of a zone of fragmented bone distal to the costochondral junction; fractures and hemorrhages were frequently observed in this area; the marrow of the shaft in this vicinity became filled with a loosely constructed gelatinous fibrillar tissue (*Gerüstmark*).

These animals served as controls. Eleven other guinea-pigs were placed on the same diet and infected simultaneously with an eighteen hour broth culture of Staphylococcus pyogenes-aureus, which was injected directly into the marrow cavity of the tibia, muscles of the leg and skin. Six of the animals showed severe local infection with sepsis of varying degrees and died between the nineteenth and and the fortieth day without any symptoms of scurvy. The bones were brittle because of osteoporosis; the liver was fatty; the spleen, large. Five animals died of scurvy between the twenty-first and the thirtieth day. In none of these was there severe local infection or sepsis.

In another experiment, Jaffe injected cultures of Staphylococcus aureus into guinea-pigs ten days after the scorbutic diet was instituted. The animals died in from seven to twelve days, much sooner than the controls. He further observed that repeated administration of staphylococcus vaccine to guinea-pigs prior to placing them on a scurvy-producing diet did not in any degree retard the development of scurvy.[46] These experiments suggested that the protective effect of staphylococcic infection in preventing the occurrence of scorbutic symptoms was probably due to the production of vitamin C by the bacterial growth. (The capacity of bacteria to produce vitamins A and B was demonstrated by Burrows and Jorstad.[47])

Baj [48] confirmed Jaffe's observations. An infection with Staph. albus does not arrest the phenomena of scurvy if the infection is induced when these are already present. If, however, the infection is induced on the same day that the animals are placed on the deficient diet, the manifestations of scurvy may be averted.

The basic diet used was the same as in Jaffe's experiments. Four groups of 12 guinea-pigs each were used. One group was placed on a scurvy-producing diet and observed. A second group was placed on the same diet and a culture of Staph. albus injected on the same day. A third group was fed a normal diet and similarly infected. A fourth group was infected after systemic scurvy was present. With the basic diet, scurvy appeared in from sixteen to eighteen days and proved fatal in from thirty to thirty-five days. In the animals that were infected at the beginning of the experiment suppuration and sepsis occurred, but

46. The diet used in Jaffe's experiments consisted of soy bean flour, 50 parts; rolled oats, 29; dried milk powder, 10; brewers' yeast, 4; butter fat, 5, and calcium carbonate and sodium chloride 1 part. The soy bean flour, oats and milk were autoclaved. In addition, the animals received hay for roughage and distilled water ad libitum.

47. Burrows, M. T., and Jorstad, L. H.: Am. J. Physiol. **77**:38, 1926.

48. Baj, J. L.: Chir. d. org. di movimento **14**:477, 1929.

the bones showed no changes in the cartilaginous zone indicative of decalcification or of medullary hemorrhages or sclerosis. The infection, however, was more severe in the scorbutic animals than in the normally fed animals.

In other types of infection, such as that with Trypanosoma Brucei, a greater need for vitamin C is evident, for infections of this type may hasten the onset of scurvy (Nassau and Scherzer [49]).

Pneumococcus.—Though guinea-pigs lacking vitamin C revealed no change in their ability to produce specific agglutinins and though there was no difference from the normal in their phagocytic mechanism as estimated by the opsonic index, their natural resistance to pneumococcic infection was lowered, according to Werkman, Nelson and Fulman.[10] Unfortunately, the data are limited. A virulent strain of Pneumococcus was injected intraperitoneally into 9 scorbutic guinea-pigs and 8 controls. There was a slight difference in the duration of life in the two groups. The scurvy-producing diet of ground oats, wheat and autoclaved milk was deficient in other vitamins as well as C. A culture of the organism employed was not used, but an emulsion of livers from infected mice. The evidence does not warrant the conclusion.

Schmidt-Weyland and Költzsch,[50] who observed spontaneous infections of scorbutic guinea-pigs with the pasteurella of fowl cholera and pneumococci, studied the incidence of induced infections with these organisms under experimentally controlled conditions.

They fed cultures of these bacteria to the experimental animals or sprayed the cultures into cages and subsequently exposed normal and scorbutic animals to infection from this source. The blood and various organs were cultured at death or at the termination of the experiment.

Of 40 normally fed guinea-pigs exposed to the cultures, only 5 died. Of 58 uninfected scorbutic animals not subjected to exposure to the cultures, 31 showed sepsis from fowl cholera and 12 sepsis from pneumococcic infection. Of 33 scorbutic guinea-pigs exposed to the spray of pneumococci and fowl cholera organisms, 27 showed sepsis from fowl cholera and 3 sepsis from pneumococcic infection. Of 5 fed the cultures by mouth, only 1 contracted pneumococcic infection. Of 9 given the mixed culture by mouth and exposed to spraying, 6 contracted fowl cholera.

Apparently, the incidence of spontaneous pasteurella or pneumococcic infection in scorbutic guinea-pigs was as high as the incidence in those in which the cultures were administered by spray or by feeding. The presence of sepsis was established by cultivation of the infecting organisms from the tissues at death. The data are confusing and difficult to evaluate. It is apparent that the incidence of spontaneous infections

49. Nassau, E., and Scherzer, M.: Klin. Wchnschr. **3**:314, 1924.

50. Schmidt-Weyland, P., and Költzsch, W.: Ztschr. f. Hyg. u. Infektionskr. **108**:199, 1928.

was greater in the scorbutic guinea-pigs than in the normally fed guinea-pigs. But the effort to determine quantitatively the degree of natural resistance of scorbutic animals to induced infections under controlled conditions failed, since the animals used were already carriers of the organisms employed.

Bacterium Coli.—Cognizant of the difficulties of studying induced acute infectious diseases in scorbutic guinea-pigs, Findlay [51] produced chronic scurvy by supplementing the basic diet with inadequate amounts of orange juice. Thus, to a diet of bran, oats and autoclaved milk, he added 2 cc. per day of orange juice. The chronic scurvy that resulted showed a major difference from acute scurvy in the changes in the marrow. The framework of the marrow persisted, but there were areas of gelatinous degeneration, consisting of homogeneous interstitial ground substance and containing blood pigment, which replaced the hematopoietic tissue. No atrophy of the lymph glands, thymus, lymphatic tissue or spleen occurred. Little difference in antibody formation as determined by serum reaction was observed.

Findlay [51] observed the effect of chronic scurvy on the natural resistance to infections induced with Pneumococcus, Staph. aureus, Streptococcus haemolyticus and Bact. coli. In these experiments he made an effort to estimate the quantity of bacterial material necessary to produce infection, the duration of life and the character of the cellular reaction to the infection.

The animals were fed the scorbutic diet during a period of six weeks. Then they were infected with a particular organism. In the case of Pneumococcus, 6 scorbutic animals died in an average period of from two to three days, while 6 normally fed animals died in from six to eight days, of the same dose of infecting organisms. In another experiment, 4 animals with scurvy died in from five to eight days after injection of smaller quantities of pneumococci, while 4 of 8 control guinea-pigs survived, and 4 died in eight days. Similar differences in the minimal lethal dose of Str. haemolyticus and Bact. coli were observed.

The guinea-pigs with chronic scurvy were killed by a quantity of bacteria estimated to be about two thirds of the quantity required to kill the normal animals. He attributed their decreased natural resistance to the degeneration of the hematopoietic system. However, no change in the blood count was observed except a very slight reduction in the number of red cells and leukocytes.

Though the number of animals in each group studied was small, the results in all the experiments were consistent.

Bacterium Aertryke.—From a study of the effect of variations in the calcium, vitamin C and vitamin D ratio in the diet on the permea-

51. Findlay, G. M.: J. Path. & Bact. **26**:1, 1923.

bility of the intestinal wall to bacteria, Grant [52] concluded that an adequate balance of these three dietary constituents is necessary to maintain the normal resistance of the intestines to the migration of bacteria into the blood stream. She believed that either an excess of vitamin D with a deficiency of vitamin C or the reverse may alter the permeability of the intestinal tract to bacteria. Similar effects of deficiency of both C and D or an excess of calcium were noted.

It is probable that an excess of cod liver oil in the diet may inhibit the utilization of vitamin C or exaggerate the effects of a scorbutic diet. The injury to the intestine by a diet deficient in vitamin C was pointed out by McCarrison,[33] who suggested that in scurvy alteration in the intercellular cement substance alters the permeability of the mucous membranes. This has never been demonstrated experimentally, however.

In her experiments, Grant [52] used a basic diet of rolled oats, timothy hay and sodium chloride. This basal diet in itself induced scurvy in 20 guinea-pigs, but in no case was there evidence of spontaneous infection with Bact. aertryke. When 3 cc. of cod liver oil was added daily for two weeks, 10 of 20 animals became spontaneously infected. In 12 guinea-pigs in which 1.5 cc. of orange juice was added to the basic diet daily no infection developed. Of 10 animals to the diet of which calcium lactate was added, only an occasional one became infected. When both calcium lactate and cod liver oil were added to the diet, about half became spontaneously infected. When calcium lactate and linseed oil were added, none became infected.

In a second series of experiments guinea-pigs were placed on these diets and 0.5 cc. of a culture of Bact. aertryke was administered orally. In those groups fed a normal diet of hay, oats, salt and cabbage plus an excess of cod liver oil, positive cultures from the organs were obtained, whereas of those fed a normal diet alone, none became infected, nor did those animals given a diet containing an excess of cod liver oil plus an excess of orange juice. The diets were all begun two weeks prior to inoculation.

Apparently, an excess of cod liver oil in an animal with an intestinal wall injured by a deficiency of vitamin C increased the permeability of the wall to bacteria, and this increase was not due to the excess of fat in the cod liver oil since similar quantities of linseed oil did not have the same effect.

In infections induced with Bact. aertryke in animals fed normal diets, an excess of cod liver oil seemed to increase the permeability of the intestine to the organism. If simultaneously an excess of orange juice was given, the deleterious effect was not manifest. It is difficult to interpret the significance of these experiments or to evaluate the results. The conditions are too complex.

Chronic Infections with Mycobacterium Tuberculosis.—A number of articles have appeared on the relation of scurvy to experimental tuber-

52. Grant, A. H.: J. Infect. Dis. **39**:502, 1926.

culosis in animals. Mouriquand, Michel and Bertoye [53] stated that tuberculosis in guinea-pigs did not modify the evolution of scurvy nor did chronic scurvy seem to accelerate the development of experimental tuberculosis. The coexistence of this infection did not increase the intensity of the scorbutic phenomena. In subsequent papers [54] in which the data are given in more detail, these investigators corroborated their earlier findings.

Of 15 guinea-pigs infected with human tubercle bacilli, 2 fed a scurvy-producing diet died in from thirty to thirty-four days with signs of severe scurvy and tuberculosis of moderate severity; 6 were fed insufficient quantities of the antiscorbutic factors furnished by dried barley and 10 cc. of sterilized lemon juice; 7 were placed on an adequate diet and given 10 cc. of fresh lemon juice daily and 10 Gm. of fresh barley. In the second and third groups, 2 guinea-pigs died accidentally on the eighth day, and 10 died in the period from the thirty-fifth to the forty-seventh day, presenting tuberculous lesions of similar intensity; these 10 included 5 from each of the two groups.

In a second series of 16 guinea-pigs infected as before, 4 were fed kennel rations, 6 barley, grass and fresh lemon juice, and the rest a diet containing an inadequate amount of antiscorbutic factors. On the sixty-first and sixty-third day they killed 3 animals from each of the three groups. The lesions were of the same intensity in all. The others died in the period from the eighty-first to the one hundred and forty-fourth day with lesions varying in intensity according to the duration of life and regardless of the diet.

In a third series, guinea-pigs were infected with the same strain of organisms and given the same diets as before. The inoculations were not made, however, until the twenty-eighth day after the diet was started. There was no difference in longevity whether the animals were fed fresh lemon juice, sterilized lemon juice or kennel rations.

These observers believed that there was no essential difference in the course of the chronic scurvy or in that of the tuberculosis which could be ascribed to the fact that both were present. Though their experiments are suggestive, the number of animals in any one group was too small to allow one to evaluate their results.

Coulard [55] observed that guinea-pigs deprived of vitamin C and inoculated with extremely small doses of tubercle bacilli were more severely affected than normally fed animals similarly infected. The appearance of the local lesion and of adenopathy was hastened, and the extension of the lesions to the spleen and viscera was more rapid.

Incident to an extended study on the effect of vitiated air on experimental tuberculosis, Sewall, Lurie, Stoifer, Silver and Woo [56]

53. Mouriquand, C.; Michel, P., and Bertoye, P.: Compt. rend. Soc. de biol. **87**:854, 1922.

54. Mouriquand, C.; Michel, P., and Bertoye, P.: Compt. rend. Soc. de biol. **88**:1043, 1923.

55. Coulard, E.: Presse méd. **31**:611, 1923.

56. Sewall, H.; Lurie, M. B.; Stoifer, I.; Silver, R., and Woo, C. T.: Am. Rev. Tuberc. **15**:328, 1927.

observed the effect of an inadequate diet on the incidence of tuberculosis in groups of guinea-pigs exposed to infected cage mates.

They divided 96 guinea-pigs into groups of 6 each. To the cage of each group they added a guinea-pig inoculated subcutaneously with 0.1 mg. of a bovine strain of tubercle bacilli. Half of the animals were fed on a vitamin-deficient diet of rolled oats, dry rye bread, timothy hay and water. The normally fed guinea-pigs when exposed to the animals with open lesions contracted tuberculosis in from three to four months. In the animals fed a diet deficient in vitamin C the interval between exposure to the tuberculous animals and death from tuberculosis was the same as in the normally fed animals.

In this series a high mortality from intercurrent pneumonia occurred, particularly in the chronically deficient group. Thus, from the tables furnished one learns that 17 died in three months, 22 in from four to five months, 34 in from eight to twelve months and 19 in from twelve to sixteen months, making a total of 92 deaths from pneumonia in the experimental period of sixteen months.

Only 5 guinea-pigs contracted tuberculosis spontaneously, and these died in from four to sixteen months after exposure. On the other hand, of the animals fed a full diet and exposed to cage mates with open tuberculous lesions, 6 acquired fatal tuberculous infection during the same period. The mortality from spontaneously acquired tuberculosis was 10 per cent as compared with 5 per cent in the group fed a diet low in vitamin C.

This type of experiment is valuable, for it simulates more closely human conditions of exposure to open tuberculosis in the community. It is regrettable that the experimental epidemiological approach is not more frequently used in studies on variations in natural resistance to such diseases as tuberculosis.[57]

An analysis of the data of Sewall and his co-workers [56] reveals certain possible sources of error. The high incidence of intercurrent pneumonic infections in both groups, particularly high in those fed the vitamin-deficient diet, tends to vitiate the experimental findings. These animals died within the first half of the year, reducing the average length of exposure of this group. Jaffe [45] and later Baj [48] showed that certain infections may inhibit scorbutic manifestations owing to the fact that some bacteria are apparently capable of producing vitamin C. The chronic pneumonic infections in guinea-pigs may serve a similar purpose. The authors have further committed an error in including among their controls all the vitamin-deficient animals that had apparently escaped tuberculous infection in the experiment. Most of these

57. The method of utilizing the experimental epidemiological approach to problems in host susceptibility to infection has been investigated by S. Flexner (J. Exper. Med. **36**:9, 1922), H. L. Amoss (ibid. **36**:25 and 45, 1922), L. T. Webster (ibid. **36**:71, 1922; **37**:21, 33, 231, 269 and 781, 1923; **38**:33 and 45, 1923; **39**:879, 1924), I. W. Pritchett (ibid. **41**:195, 1925) and W. W. C. Topley (J. Hyg. **19**:350, 1920; **20**:103, 1921; **21**:20, 226, 237 and 243, 1922) in mouse typhoid and rabbit snuffles, and by D. Perla (J. Exper. Med. **45**:209, 1927) and M. Lurie (ibid. **51**:729, 743 and 769, 1930) in tuberculosis.

controls had already been exposed for more than ten months to contact with guinea-pigs having active tuberculosis. It appears from the tables that practically all the controls were from this source, though this is not clearly stated. This is obviously an unfair control, for animals already fed deficient diets for a year cannot be assumed to become normal when restored to a normal diet. In fact, the authors stated that in spite of a full diet 6 or 8 of the controls within two years presented keratitis and other manifestations of vitamin deficiency. Finally, the significant observation made incidentally in the text of their work that the males in the group on the deficient diet showed no evidence of fighting among themselves whereas the normally fed animals had severe lesions on their backs due to conflict suggests that in the deficiently fed animals there was a general decrease in their interest in the environment. Such apathetic members would be less likely to express interest in an ulceration of their tuberculous cage mate, which was the source of infection, and their chances of infection would therefore be less than those of the robust animals fed on a normal diet.

For these reasons the findings of Sewall and his co-workers [56] cannot be accepted as throwing light on the problem of the relation of chronic insufficiency of vitamin C or of vitamins in general to natural resistance to infection.

Recently the rôle of chronic deficiency of vitamin C in the pathogenesis of tuberculosis in the guinea-pig was studied by Greene, Steiner and Kramer.[58]

The diet partially deficient in vitamin C consisted of a mixture called sobee (soy bean flour, olive oil, arrowroot starch, dicalcium chloride, dextrimaltose), 76 per cent; one termed alacta (butterfat, protein, lactose, salts), 20 per cent, brewers' yeast, 3 per cent, and cod liver oil, 1 per cent. For inoculation, the Saranac Laboratory strains of Myco. tuberculosis H_{37} and R_1 were used. Guinea-pigs fed diets completely deficient in vitamin C died within from four to five weeks. When the diet was supplemented with small amounts of an antiscorbutic substance, the animals were maintained in a state of chronic scurvy for several months. Chronic deficiency of vitamin C combined with progressive tuberculous infection caused significant shortening of the period of survival. Chronic scurvy did not cause development of generalized tuberculosis in animals infected with the relatively avirulent R_1 strain. When infection with strain H_{37} or with bacilli in sputum from tuberculous patients was obtained by the subcutaneous or the enteric route, the infection became generalized more rapidly in the animals that were chronically deficient in vitamin C than in the normally fed guinea-pigs.

Intestinal lesions were apparently more frequent in the vitamin-deficient group than in the control group. It is interesting that the

58. Greene, M. R.; Steiner, M., and Kramer, B.: Am. Rev. Tuberc. **33**:585, 1936.

tuberculous intestinal lesions were more extensive when sputum was fed than when pure cultures of tubercle bacilli were administered.

However, guinea-pigs infected with tubercle bacilli and allowed to become acutely scorbutic showed tuberculosis in no greater degree than guinea-pigs given a normal diet.

The evidence for these conclusions is too detailed to recount. Though sufficient numbers of animals were employed in each group to permit the observation of significant variations, the application of the methods of statistical analysis to such small groups appears unjustifiable. From the data presented, the differences in the extent of the lesions in various groups, though objectively stated, cannot be quantitatively estimated. The data do not seem to justify the conclusion that generalized tuberculosis developed more rapidly in the chronically scorbutic animals than in the controls.

Heise and Martin [59] studied the excretion of vitamin C in 44 cases of minimal, moderately advanced and far advanced human tuberculosis. The method of Harris, Ray and Ward [48] for the estimation of vitamin C in urine by titration against dichlorophenolindophenol was used. It was roughly found that the more advanced and active the tuberculosis, the less was the daily excretion of cevitamic acid.

In another group of cases, 55 mg. of cevitamic acid in the form of 4 ounces (118 cc.) of orange juice was administered daily for two weeks. The increase in the cevitamic acid excreted was noted. The increase was considered positive if it exceeded 16 mg. daily. In all of the patients with inactive tuberculosis, it was positive; in 80 per cent of those with active disease, it was negative. The authors stated (erroneously) that the amounts of cevitamic acid required daily by normal healthy persons vary from 15 to 20 mg. whereas the amounts required daily to bring tuberculous patients into equilibrium range from 55 to 138 mg. and in some instances as high as 200 mg. Apparently, an increased requirement of the vitamin is manifested in tuberculosis, and the daily excretion seems to parallel the activity of the disease.

Trypanosoma Brucei.—In infection with T. Brucei in guinea-pigs, the symptoms of scurvy occur at an earlier period in animals fed a vitamin-deficient diet than in uninfected animals similarly fed (Nassau and Scherzer [49]). Five guinea-pigs infected with T. Brucei and then placed on a vitamin-free diet showed signs of scurvy within from ten to eleven days and died within from eighteen to twenty-two days. Four control uninfected guinea-pigs similarly fed did not begin to show scorbutic manifestations until the eighteenth day and died within twenty-

59. Heise, H., and Martin, G. J.: Proc. Soc. Exper. Biol. & Med. **34**:642, 1936.

three days. In T. Brucei infections there is a greater demand for vitamin C, and apparently this organism cannot synthesize vitamin C.

No essential difference in the severity of the infection in the scorbutic animals as determined by trypanosomal counts was indicated, though the duration of life was shortened by the deficiency of vitamin C in the diet. The details of the experiment in this regard are not clearly indicated. The animals with scurvy lost markedly in weight during the infection; the normally fed infected guinea-pigs did not.

Typhus Fever.—Guinea-pigs and rats subjected to vitamin deficiency and then, when symptoms appeared, inoculated with typhus virus exhibited clinical pictures which indicated far more severe infection than that observed in normal animals after inoculation (Zinsser, Ruiz Castañeda and Seastone [60]). There were also wider distribution and greater concentration of rickettsiae, amounting in the pleural and peritoneal exudates almost to cultural proportions.

These experiments were carried out in an effort to obtain large amounts of rickettsiae suitable for immunologic studies. Thirteen guinea-pigs were fed a diet of rolled oats, skimmed milk (autoclaved for one hour) and water during a period of from fourteen to twenty days and then inoculated intraperitoneally with tunica vaginalis from animals suffering with Mexican typhus. In many of the guinea-pigs the disease ran a severe course, and rickettsiae were recovered in abundance from tunica and peritoneum. The animals, of course, were scorbutic, but the authors do not attribute the result to a lack of any one vitamin since all were absent from the diet.

A small number of rats on a similar vitamin-free diet for fourteen days likewise showed marked susceptibility to induction of typhus. Rickettsiae were recovered from visceral scrapings and were found in the spleen, liver, blood, pia mater and endocardium in normally fed rats. The infection was very mild.

These experiments demonstrate the drop in natural resistance that follows complete vitamin deficiency but do not indicate the specific effect of deprivation of vitamin C. Vitamin deficiency is one of the important factors responsible for the high mortality from typhus historically observed during periods of war and famine (Zinsser and others [60]).

Fungus Diseases.—Guinea-pigs were fed a diet deficient in vitamin C, consisting of alfalfa, rolled oats, purified casein and salt, during a period sufficient to produce early manifestations of scurvy. They

60. Zinsser, H.; Ruiz Castañeda, M., and Seastone, C. V., Jr.: J. Exper. Med. **53**:333, 1931.

were then given intratracheally and per os daily cultures of Monilia albicans. Although the cells of M. albicans were found in the lung as long as seven days after inoculation, their presence was only sometimes associated with pathologic changes. The fungus was not limited to scorbutic animals but was equally prominent in normal animals. Apparently, deficiency in vitamin C does not alter the susceptibility of the guinea-pig to infection by M. albicans.

Rheumatic Fever and Scurvy.—In the guinea-pig chronic scurvy plus superimposed infection with beta streptococci and to a lesser extent chronic scurvy alone produce arthropathy with pathologic similarities to rheumatic fever and rheumatoid arthritis, according to Rinehart, Connor and Mettier.[61a] These workers stated that lesions produced in the heart valves by combined scurvy and infection were similar to those of rheumatic fever. From their observations they suggested that subclinical degrees of scurvy may predispose to rheumatic infection in human beings.

In their experimental studies on guinea-pigs the diet used consisted of skimmed milk, ground oats and bran, butterfat, dried yeast, cod liver oil, sodium chloride and ferrous lactate. As the infecting agent, they used a strain of hemolytic streptococci (obtained from a guinea-pig) which produced subacute lymphadenitis. The animals were placed on the diet deficient in vitamin C for a period of twenty-two days prior to the injection of the bacteria. Definite arthropathy was found in the scorbutic animals, but more definite arthropathy, in the infected scorbutic animals. In the guinea-pigs with chronic scurvy, eosinophilic hyaline material was present in the joint spaces and especially in the periarticular subsynovial layers.

In other studies they noted that infection in guinea-pigs maintained on an adequate diet usually produced no significant lesions in the heart valves. When such lesions occurred, they were of an exudative rather than proliferative type. In uncomplicated scurvy, definite atrophic and degenerative changes occurred in the collagenic stroma of the heart valves. In scurvy with added infection (beta streptococci), striking lesions of a combined degenerative and proliferative character developed in the heart valves with considerable frequency. These lesions, they believed, closely resembled the endocarditis of acute rheumatic fever. Further, degenerative and proliferative lesions of the heart muscle and pericardium occurred in the experimental animals subjected to combined scurvy and infection, similar in type to the Aschoff reaction. The authors did not insist that organisms other than the beta streptococcus may not, in the presence of scurvy, produce similar lesions. They called attention, however, to the fact that a basic lesion in both conditions is a degenerative change occurring in collagen. Lesions resembling the "fibrinoid degeneration" of Klinger were seen in various sites in animals subjected to combined scurvy and infection.

Though not questioning the presence of infection as a factor in rheumatic fever, Rinehart, Connor and Mettier [61] suggested that there

61. (*a*) Rinehart, J. F.; Connor, C. L., and Mettier, S. R.: J. Exper. Med. **59**:97, 1934. (*b*) Rinehart, J. F., and Mettier, S. R.: Am. J. Path. **9**:932, 1933.

is a considerable amount of evidence that some factor in addition to simple infection contributes to the development of this disease. Experimentally, infection alone or scurvy alone did not produce significant lesions, but when these were combined, striking lesions were produced, particularly of the heart valves.

To further the argument that a condition of undernutrition in vitamin C may be a necessary background for the development of rheumatic fever, Rinehart and his collaborators have presented epidemiological and clinical data that are suggestive of this contention and intriguing in their implications. They [62a] have reported that the blood plasma cevitamic acid (reduced) of patients with active rheumatoid arthritis is regularly low if the patients have not been maintained on a diet with a supplement high in vitamin C. The low level rises in response to extra supplements of vitamin C. But in many this rise is refractory; that is, the intake required to maintain an adequate level of vitamin C in the plasma is much above the average requirement for normal persons. The investigators can offer no explanation for this.

In 21 cases of acute rheumatic fever, they [62b] found the level of the reduced cevitamic acid in the blood plasma to be uniformly lowered.

Rinehart, Connor and Mettier [61a] pointed out that the debilitated state of the prerheumatic child has been emphasized clinically and that rheumatic fever is a disease of the poor and undernourished. Campbell and Warner [63] and Swift [64] found that rheumatic fever is from fifteen to twenty times more frequent in the laboring classes than in the middle and upper classes and most frequent among poor children of elementary school age living in the city. Göthlin,[65] using reduced capillary strength as an index of latent scurvy, found evidence of undernutrition in vitamin C in 18 per cent of the school children in the provinces of Upland, Sweden, during August and May, a time when rheumatic fever is at its height. In Norrbotten, in the arctic, Falk, Gedda and Göthlin [66] observed a similar incidence of latent scurvy in presumably healthy children. Dalldorf,[67] using capillary resistance tests, found that mild

62. (*a*) Rinehart, J. F.; Greenberg, L. D., and Baker, F.: Proc. Soc. Exper. Biol. & Med. **35**:347, 1936. (*b*) Rinehart, J. F.; Greenberg, L. D., and Christie, A. U.: ibid. **35**:350, 1936.

63. Campbell, M., and Warner, E. C.: Lancet **1**:61, 1930.

64. Swift, H. F.: Am. Heart J. **6**:625, 1931.

65. Göthlin, G. F.: Skandinav. Arch. f. Physiol. **61**:225, 1931.

66. Falk, G.; Gedda, K. C., and Göthlin, G. F.: Upsala läkaref. förh. **38**:11, 1932.

67. Dalldorf, G.: Am. J. Dis. Child. **46**:794, 1933.

degrees of deficiency in vitamin C may constitute a problem of importance to the public health since it occurs in as high as from 35 to 65 per cent of the school population. Children from 5 to 14 years of age require an intake of vitamin C twice that of adults. It is a matter of common knowledge that latent scurvy and rheumatic fever occur late in winter and early in spring, during the period of diminished availability of vitamin C. The vitamin C content of winter milk is very low.

The geographic distribution of rheumatic fever has been carefully studied, and its absence in the tropics, where scurvy is indeed a rare disease, is conceded by numerous observers. Seegal and Seegal [68] in a study of the geographic distribution of rheumatic fever in Canada and the United States showed that the incidence diminishes as the tropics are approached. In an experience with 150,000 patients in the true tropics Clark [69] observed no rheumatic fever, mitral stenosis or chorea.

That diet is of importance in the predisposition to rheumatic fever is suggested by the fact, reported by van Breemen,[70] that this disease is uncommon in Holland, where the dietary is presumably rich in foods containing vitamin C.

The long and sterile search for an etiologic agent of rheumatic fever has led into the treacherous fields of endless controversy. The reproduction of the disease in animals has been simulated repeatedly, but there is no agreement concerning the etiology. It may well be that the work of Rinehart and his associates [71] indicates a possible explanation of the difficulties hitherto encountered.

However, it may be stated at this point that from the point of view of comparative pathology the lesions produced by Rinehart and his associates [61] were not identical with those observed in rheumatic fever in human beings, nor was the disease similar in its clinical course to that termed rheumatic fever. Their work, however, adds support to the contention that chronic scurvy enhances the allergic response of the body to antigenic substances. Such manifestations of myocardial and joint reactions in guinea-pigs and rabbits are nonspecific and are observed in a large variety of allergic and toxic states in these animals.

It would be worth while to carry their suggestion into the field of preventive medicine and gage the effect of adequate vitamin C in the diet of the children in a community on the incidence of rheumatic infection over a period of ten years.

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68. Seegal, D., and Seegal, B. C.: J. A. M. A. **89**:11, 1927.
69. Clark, J. T.: J. Trop. Med. **33**:249, 1930.
70. van Breemen, J.: M. J. & Rec. **128**:469, 1928.
71. Rinehart and others.[61]

Schultz,[72] in a recent study on the utilization of cevitamic acid in rheumatic fever, made careful determinations of the excretion of vitamin C in the urine according to a quantitative method devised by Sendroy and Schultz.[73] He was unable, however, to detect any evidence of a deficiency of this acid in patients with rheumatic fever. Of the 13 patients studied at the height of their infection, 8 were found to have relatively deficient, 4 normal and 1 above normal excretion of cevitamic acid.

Sendroy and Schultz felt that the urinary excretion of cevitamic acid was a fair index of the availability of vitamin C, since it is dependent on the relative state of saturation of the tissues and the quantity absorbed from the ingested food. If the intake can be kept constant by the ingestion and absorption of a fixed dose of cevitamic acid, the results may be reliably interpreted as a measure of the state of saturation of the tissue.

In 5 of the patients examined, the results were unfortunately invalidated by vomiting. In 8 patients there was apparent deficiency of cevitamic acid; in only 2 could this be ascribed to the diet. Schultz did not feel that this evidence supported the contention that deficiency in cevitamic acid is a predisposing factor in the causation of rheumatic fever.

In subsequent studies he reported the use of cevitamic acid in the prevention of rheumatic activity and in the treatment of rheumatic infection. He had observed increased capillary permeability in many children suffering from rheumatic fever. Though this test may imply the presence of subclinical scurvy, the condition is found in other febrile states as well as in rheumatic infections. He admitted, however, that this increase in permeability was an expression of dietary deficiency rather than of a rheumatic state, because no characteristic change in the capillary permeability accompanied the onset or disappearance of signs of rheumatic activity. The frequency of change of capillary permeability coincident with rheumatic carditis and other febrile states has been reported by Stephan,[74] Cutter and Marquardt [75] and Dalldorf.[67]

Of 56 patients between the ages of 4 and 19 in whom attacks of rheumatic fever had occurred in previous years, 28 were given cevitamic acid in amounts of 100 mg. daily. The control group was given the same amount of lactose by mouth. This quantity of cevitamic acid, Schultz

72. Schultz, M. P.: J. Clin. Investigation **15**:385, 1935.

73. Sendroy, J., and Schultz, M. P.: J. Clin. Investigation **15**:369, 1936.

74. Stephan, R.: Berl. klin. Wchnschr. **58**:317, 1921.

75. Cutter, I. S., and Marquardt, G. H.: Proc. Soc. Exper. Biol. & Med. **28**:113, 1930.

believed, was sufficient to protect against scurvy, in view of the estimated minimal daily requirement of from 50 to 60 mg. for children (Falk, Gedda and Göthlin [66]).

The capillary fragility was determined at frequent intervals by means of a suction method similar to that described by Johnson. By this method the effects on the surface of the skin of negative pressures within a suction cup at intervals of 10 mm. of mercury are determined. The reading which is recorded is the lowest negative pressure at which capillary hemorrhages appear.

Though the patients of the one group were treated with cevitamic acid over a period of a year, no apparent differences were observed in either of the two groups. There was, however, definite improvement in capillary permeability in the group treated with cevitamic acid.

In a second series of 20 patients with active rheumatic fever, cevitamic acid was used as a therapeutic agent; 17 patients each received 250 mg. of cevitamic acid daily by mouth or intravenously for from one to five months, and 7, 200 cc. of orange juice by mouth daily.

Though the diet was supplemented further with yeast and cod liver oil, none of these measures exerted a demonstrable effect on the clinical picture of the fever. Schultz [72] concluded that the clinical manifestations of acute rheumatic fever are not demonstrably affected by additions of vitamin C as cevitamic acid or as orange juice to the dietary or by intravenous injections of cevitamic acid over several months. He did not believe that deficiency in cevitamic acid is a necessary factor in the etiology of rheumatic fever, or that adequate intake of this acid over several months prevents the occurrence of rheumatic fever in patients who otherwise would be expected to have the disease.

Incidental to a consideration of the question of the rôle of a deficiency of vitamin C in the etiology of a number of pathologic conditions other than scurvy, Finkle [42b] observed the excretion of this vitamin before and after intravenous injections of the vitamin in 14 patients with rheumatic fever. Though most of the patients showed before the injections low levels of excretion of the vitamin in the urine, in 5 there was a considerable increase in the output of vitamin C following the injections of cevitamic acid. He believes that there was no disturbance of the metabolism of this vitamin in these patients. It is of interest that of 24 patients with rheumatoid arthritis, only 4 showed a normal curve of excretion of vitamin C in the urine. The remainder of the group either had excretion levels below the normal or showed no rise following the administration of cevitamic acid.

We do not feel that the clinical experiments reported by Schultz,[72] Sendroy and Schultz [73] and Finkle [42] definitely negate the hypothesis of Rinehart and his co-workers [61a] that vitamin C is a factor in the

causation of rheumatic fever. There are several fallacies in their deductions:

1. It is admitted by them that a large number of patients with latent or active rheumatic fever present evidences of subclinical scurvy, as determined by capillary fragility tests and by diminished excretion of cevitamic acid. The fact that the rheumatic patient is capable of utilizing vitamin C as the normal person is, as determined by studies, seems to be totally irrelevant since patients suffering from severe scurvy are also capable of utilizing vitamin C.

2. In the second place, the administration of cevitamic acid or of orange juice in amounts hardly twice the minimal protective antiscorbutic dose does not seen to us to insure an adequate excess either in the prophylaxis or in the treatment of rheumatic infection. For, in spite of the disappearance of symptoms of subclinical scurvy, can one be certain of what constitutes the optimal physiologic requirement of the body? This particularly applies to the problems of resistance to infection.

3. The failure of the administration of cevitamic acid either to decrease the incidence of recurrences in latent rheumatic fever or to cure rheumatic infection when it is already present does not, in our opinion, in itself negate the hypothesis that deficiency of vitamin C may be an etiologic factor in rheumatic fever. The contribution of Rinehart and his associates [71] is not that rheumatic fever is caused by deficiency of vitamin C but that an organism such as a streptococcus, which may be the immediate bacterial moment of the disease, can gain a foothold in persons who have had a prolonged relative insufficiency of this vitamin. It is possible that, once a rheumatic infection is established, the restoration of normal availability of vitamin C will not affect the carditis or prevent recurrences of the infection which is entrenched in the organism.

4. Finally, one must not lose sight of the fact that prolonged insufficiency of a vitamin may irreparably injure the organism to a point at which restoration of the normal state may never occur in the life span of the organism. This has been demonstrated in the case of vitamin A by Sherman and MacLeod,[76] who observed that relative deficiency of vitamin A early in the life of an animal may severely injure the mechanism of resistance and that this injury will persist for many years after the dietary deficiency has been rectified.

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76. Sherman, H. C., and MacLeod, F. L.: J. Am. Chem. Soc. **47**:1658, 1925.

The ideal clinical experiment to test the validity of Rinehart's hypothesis would be to compare the incidence of rheumatic fever in children raised from birth on a diet adequate in vitamin C with the normal incidence of the disease in the community.

Summary.—Certain bacteria are apparently capable of synthesizing vitamin C. Subacute infection with staphylococci may inhibit the occurrence of scurvy in animals fed a diet deficient in vitamin C.

The experimental data are confusing as to the effect of deficiency of vitamin C in the diet on natural resistance to subsequently induced or coexisting acute bacterial infection. Much of the work does not bear critical analysis. The conclusions are often unsubstantiated by the experimental evidence offered. The conditions of the experiments reported are frequently too involved and complicated.

Though it is probable that the incidence of spontaneous infection with the pasteurella of fowl cholera may be greater in scorbutic than in normally fed guinea-pigs, it is not definitely established that scurvy lowers the natural resistance to this infection. There is a suggestion that scorbutic guinea-pigs succumb to acute infection with Str. haemolyticus, Bact. coli, Staph. aureus or Pneumococcus in shorter periods of time and required slightly lower minimal quantities of these organisms to become fatally infected than normally fed animals. The differences, however, with the exception of Pneumococcus, are not statistically significant.

Under certain conditions, vitamin C deficiency increases the permeability of the intestinal wall to bacteria, such as Bact. aertryke.

The evidence as to the effect of deficiency of vitamin C in the diet on the natural resistance of guinea-pigs to subsequently induced or coexistent tuberculous infection is contradictory. It seems a priori impossible to establish significant differences in the duration of a chronic infection induced in an animal with acute scurvy.

It is reported that guinea-pigs fed a diet inadequate in vitamin C and subsequently exposed to cage mates with open tuberculous lesions (skin ulcerations) show no greater incidence of contact infection than do normally fed animals. The data and conditions of the experiments, however, are such that they throw no light on the important problem of the effect of chronic scurvy on the susceptibility of an animal to tuberculous infection.

In the guinea-pig with chronic scurvy, infection with certain organisms, such as the beta streptococcus, induces arthropathy with endocardial and myocardial lesions resembling those of rheumatic fever in human beings. It is suggested that undernutrition in vitamin C lowers the natural resistance of man to rheumatic infection and that such a nutritional factor may play a significant etiologic rôle in this disease.

In brief, complete deficiency of vitamin C in the diet may lower natural resistance to subsequently induced acute infection. The experimental evidence, however, is still inadequate and requires further confirmation.

It has not been unequivocally established what effect chronic insufficiency of vitamin C in the diet has on natural resistance to a subsequently induced chronic infection, such as tuberculosis.

Chronic insufficiency of vitamin C in the diet lowers the natural resistance of the guinea-pig to a subsequently induced infection with the beta streptococcus, and a condition simulating rheumatic infection may result.

(To be concluded)

Notes and News

Medicolegal Conference.—A state conference for the consideration of improvements in the medical and legal aspects of the administration of justice was held in Indianapolis, Dec. 4, 1936. The conference was sponsored by the medical school and the institute of criminal law and criminology of the state university, the state police department and the Indiana Committee, which consists of a group of citizens interested in law administration.

Forensic Medicine.—The formal announcement has been made by Harvard University of a gift by Mrs. Frances Glessner Lee of Chicago to establish the "George Burgess Maggrath Endowment for Legal Medicine" in the Harvard University Medical School.

In New York University the department of forensic medicine has been reorganized under the direction of Harrison Martland, who succeeds Charles Norris as professor of forensic medicine. In addition to undergraduate work, graduate instruction will be offered leading to the degree of Med. Sc. D. as well as short intensive courses in specialized branches of medicolegal work. The Charles Norris fellowship in forensic medicine has been established, which is open to candidates for work toward the degree.

University News, Promotions, Resignations, Appointments, Deaths, etc.—Simon Flexner, director emeritus of the Rockefeller Institute for Medical Research, has been elected a foreign associate of the Academy of Sciences, Institute of France.

Arthur Rudolph Mandel, professor of clinical pathology, New York University College of Medicine, died suddenly in March. He was 59 years old.

Robert M. Moore, assistant professor of pathology, University of Missouri School of Medicine, has been appointed professor of pathology and director of clinical laboratory diagnosis in the University of Mississippi School of Medicine, effective September 1, it is reported.

Milton J. Greenman, director of the Wistar Institute of Anatomy, Philadelphia, and noted for his anatomic researches, has died at the age of 70 years.

Society News.—The next annual meeting of the American Association of Pathologists and Bacteriologists will be held in Atlantic City, May 3, and 4, 1938, in conjunction with the Congress of American Physicians and Surgeons.

Abstracts from Current Literature

To Save Space the Original Titles of Abstracted Articles Sometimes Are Shortened

Experimental Pathology and Pathologic Physiology

Experimental Coronary Occlusion. R. Tennant and others, Am. Heart J. **12**:168, 1936.

Occlusion of the left anterior descending coronary artery and accompanying veins in dogs results in an increase of the lactic acid and a decrease of the glycogen content of the muscle deprived of its circulation. When the circulation is reestablished for two hours by release of the ligatures after varying intervals of occlusion, the lactic acid content of the affected muscle returns to normal, but the glycogen lost is not restored. When the circulation in the myocardium is restored by release of the ligature, a series of changes is observed histologically that contrast with the usual experimental infarction. Striking anatomic changes were noted in the myocardium supplied by the previously ligated vessels except in a heart in which the vessel was tied for only one-half hour, in which no demonstrable changes were seen. In the other hearts the myocardium supplied by the ligated vessels was the seat of an extensive hemorrhagic infarct which extended through the entire thickness of the wall, involving intensely the inner half and also the anterior third of the interventricular septum.

From the Authors' Summary.

Metaplasia of Uterine Epithelium in Rats After Administration of Estrin. C. S. McEuen, Am. J. Cancer **27**:91, 1936.

In castrate female rats, intra-uterine or continued subcutaneous injections of a solution of estrogenic substance in oil frequently produced squamous metaplasia of the uterine epithelium, with downgrowth into the stroma. In experiments previously reported and continued for several months this transformation has not progressed beyond the stage previously described. Metaplasia of the uterine epithelium did not follow direct application of 1, 2, 5, 6-dibenzanthracene, gas-house tar or pregnandiol, although the two first named are known to be carcinogenic. Neither subcutaneous injections nor direct application of the estrogenic substance produced metaplasia of the epithelium of any sex gland in male rats.

From the Author's Summary.

Experimental Radium Poisoning. M. Rosenthal and E. J. Grace, Am. J. M. Sc. **191**:607, 1936.

The general features of radium poisoning as observed in man have been reproduced in rabbits by oral administration of radium sulfate. Jaw necrosis, a characteristic of the early stages of acute radium poisoning in dial painters, can be produced experimentally by means of radium alone, without mesothorium. In the marrow, striking changes are produced, consisting of early hyperplasia of the erythropoietic elements, followed by decreased maturation of the erythrocytes and replacement of these elements by myelocytes. Finally this hyperplastic marrow is replaced by fibrous tissue. In the lymph nodes there is initial stimulation of the stem cells with subsequent damage to these cells, resulting in depletion and atrophy of the lymphoid tissue. In the circulating blood absolute lymphopenia is found. The development of myeloid tissue in the lymph nodes and spleen and the extreme myelocytic hyperplasia in the marrow of these animals suggest that the leukemia of persons who work with roentgen rays and radium may not be a pure coincidence.

From the Authors' Summary.

A Paralysis Syndrome Produced in Rabbits and Guinea-Pigs by Extracts of Normal Primate Bone Marrow. R. A. Kelser and L. S. King, Am. J. Path. **12**:317, 1936.

Extracts from the bone marrow of man and monkeys produce paralysis on intracerebral injection into rabits and guinea-pigs. Extracts from the lymph nodes in Hodgkin's disease and from the spleen in leukemia may also cause paralysis. The local effect at the site of the injection is that of a destructive agent, but the action at a distance involves primarily the cerebellum, where there are severe injury of the Purkinje cells, scattered changes in the ganglion cells, swelling of microglia and meningeal infiltration, especially with mononuclear cells. The symptoms in the animals are regarded as due to widespread functional involvement of the nervous system.

The Histology of Experimental Mumps in the Monkey. C. D. Johnson and E. W. Goodpasture, Am. J. Path. **12**:495, 1936.

In experimental mumps the essential lesion is the result of a focal action of the mumps virus on acinar epithelial cells, resulting in degeneration and necrosis of these cells. The inflammatory cellular response is secondary to the specific injury and consists of an infiltration of the area by mononuclear phagocytic cells and later by various types of lymphocytes. Polymorphonuclear leukocytes play no part in the reaction. Dissemination of lesions within the infected gland follows. The edema is probably dependent on a diffuse vascular injury secondary to the focal parenchymal lesions. Healing takes place by removal of the débris and regeneration of the acinar epithelium, which restores the gland without scarring. Inclusions in the affected epithelial cells are described and are interpreted as specific. It is concluded that in all probability similar lesions underlie mumps in human beings.

From the Authors' Summary.

Primary Idiopathic Thrombophlebitis. Nelson W. Barker, Arch. Int. Med. **58**:147, 1936.

Idiopathic or primary thrombophlebitis is a definite clinical entity. A study of seventy-nine cases showed that there are two types : first, a recurrent inflammatory lesion which tends to involve segments chiefly of small and medium-sized veins and occurs most commonly among young and middle-aged males; second, thrombophlebitis of medium-sized and large veins, which is accompanied by less inflammation and occurs as a single episode, without particular preponderance as to age or sex. Recurrent idiopathic thrombophlebitis is histologically similar to thrombo-angiitis obliterans. Cultures of affected venous segments that were obtained for biopsy showed nothing abnormal. The patients in the series of cases studied revealed a high incidence of definite focal infection in the tonsils, teeth and prostate gland. Pulmonary infarction occurred in 30 per cent and fatal pulmonary embolism in 5 per cent. Chronic venous insufficiency of a limb occurred in approximately half of the patients with recurrent and in two thirds of the patients with nonrecurrent thrombophlebitis.

From the Author's Summary.

Morphologic Changes in the Heart in Experimental Myxedema. B. Webster and C. Cooke, Arch. Int. Med. **58**:269, 1936.

Myxedema was readily produced in adult rabbits by removing their thyroid glands. The more severe involvement was accompanied by pericardial and peritoneal effusions. The heart muscle had an average fluid content of 81.9 per cent as compared with 75.6 per cent in a normal control series. On microscopic examination it showed marked degenerative changes, namely, decrease in the number of fibers, edema and disappearance of the perinuclear sarcoplasm. Myxedema is apparently capable of producing serious myocardial damage in the adult rabbit.

From the Authors' Summary.

RELATION OF THE CEREBRUM TO THE CEREBELLUM. C. D. ARING and J. F. FULTON, Arch. Neurol. & Psychiat. **35**:439, 1936.

The results obtained by Aring and Fulton may explain such baffling phenomena as the cerebellar signs in lesions of the frontal lobe or the flaring up of latent cerebellar defects following cerebral lesions. The authors experimented on monkeys and baboons. They removed the cerebellum alone; they removed the cerebellum and extirpated the cortical motor areas either unilaterally or bilaterally; they combined unilateral ablation of motor and premotor areas with section of the contralateral superior cerebellar peduncle (and vice versa), or they removed the cerebellum and produced lesions of frontal association areas. The notable observations were as follows: Destruction of the premotor area in a decerebellate animal causes accentuation of the cerebellar signs (tremor, dysmetria, broad-based gait, staggering station, etc.), but when the premotor area is intact, the cerebellar deficit is compensated. Unilateral extirpation of the motor area (area 4) after a contralateral cerebellar lesion temporarily abolishes tremor and "depresses all signs of cerebellar deficit," while destruction of frontal association areas plays no part in the compensation for the latter, i. e., does not decrease or abolish the cerebellar signs previously established.

G. B. HASSIN.

SHOCK: THE MECHANISM OF DEATH FOLLOWING INTESTINAL OBSTRUCTION. V. H. MOON and D. R. MORGAN, Arch. Surg. **32**:776, 1936.

There is much evidence that death following intestinal obstruction results from circulatory failure of the shock type. The physiologic disturbances following intestinal obstruction are those usually seen in the shock syndrome. The gross and microscopic visceral changes are identical with those which accompany shock produced by various means. These changes are: marked distention and engorgement of the capillaries and venules in the viscera, edema and ecchymoses of the lungs and gastro-intestinal mucosae and effusions into serous cavities. Evidence of injury to the capillaries is seen in the capillary hemorrhages, the formation of edema fluid of high protein content and the rapid escape of colloidal dyes from the blood into the tissues. The probable cause of the shock syndrome following intestinal obstruction is intoxication by histamine, by other products of injured tissue and by bacteria and their products absorbed from the obstructed bowel. Any of these agents alone will produce the syndrome in animals. Debate concerning the relative clinical importance of these agents is not profitable. Intestinal obstruction is one of the many conditions which produce characteristically the shock syndrome.

FROM THE AUTHORS' SUMMARY.

RÔLE OF THE RETICULO-ENDOTHELIAL SYSTEM IN THE DEPOSITION OF COLLOIDAL AND PARTICULATE MATTER IN ARTICULAR CAVITIES. J. G. KUHNS and H. L. WEATHERFORD, Arch. Surg. **33**:68, 1936.

Colloidal and particulate matter is carried to articular cavities from the various tissues of the body, such as the skin and the gastro-intestinal tract, through the blood stream. The transported material is stored chiefly in histiocytes in the synovial membrane. Large amounts are stored in the bone marrow. Lesser amounts are seen in the intermuscular septums and in the articular fat pads. Mild inflammation in articular tissues tends to increase the deposits of such transported substances. Local blocking of the reticulo-endothelial system is transitory, incomplete and ineffective in preventing the deposition of colloidal and particulate matter in articular tissues.

FROM THE AUTHORS' SUMMARY.

PATHOLOGIC CHANGES IN ADRENALECTOMIZED DOGS, PARTICULARLY IN THE ANTERIOR LOBE OF THE HYPOPHYSIS. W. M. NICHOLSON, Bull. Johns Hopkins Hosp. **58**:405, 1936.

No histologic difference between adrenalectomized and normal dogs could be determined in the anterior lobe of the hypophysis. No characteristic lesions were

found in dogs after total extirpation of the adrenal glands. In three patients with Addison's disease and atrophy of the adrenal cortex there was reduction in the number of basophils in the hypophysis, with appearance of abnormal basophilic cells. In four patients with Addison's disease and tuberculosis of the adrenal glands there was no reduction in the basophils in the hypophysis. The suggestion is made that Addison's disease, when associated with cortical adrenal atrophy, begins primarily in the anterior lobe of the hypophysis.

FROM THE AUTHOR'S SUMMARY.

INFLUENCE OF INFECTION AND INTOXICATION ON HEMOGLOBIN PRODUCTION IN ANEMIA. F. S. ROBSCHEIT-ROBBINS and G. H. WHIPPLE, J. Exper. Med. **63**:767, 1936.

In anemia in human beings, infection is often believed to be responsible. It is also generally believed that lack of absorption and definite destruction of blood are responsible. Acceleration of the metabolism produced with thyroid or dinitrophenol does not modify the hemoglobin production in standard anemic dogs. Endometritis lasting over many weeks profoundly reduces the production of hemoglobin in standard anemic dogs. A sterile abscess also will diminish the production of new hemoglobin in the anemic dog when liver is being fed, but particularly during periods of fasting, when the usual abundant production of new hemoglobin is reduced to zero. Impaired absorption can be excluded as a factor of any significance in certain given experiments. Destruction of red cells can likewise be excluded as a factor of any significance in certain given experiments. These experiments point to a disturbance of internal metabolism related to the building of hemoglobin as responsible for the inhibition of the production of hemoglobin under these conditions. We believe this same factor is often of importance in human disease.

FROM THE AUTHORS' SUMMARY.

EFFECTS OF REMOVAL OF THE FUNCTIONING GALLBLADDER. G. S. BERGH, P. SANDBLOM and A. C. IVY, Surg., Gynec. & Obst. **62**:811, 1936.

Among the changes in the biliary system of the dog following cholecystectomy are slight hepatitis, dilatation of the biliary ducts and disturbance of the choledochoduodenal sphincter. Incompetence of the sphincter of Oddi may allow transmission of pressure into the common duct from the duodenum. Such transmitted pressure must be considered as a possible factor in the dilatation of the biliary ducts following cholecystectomy.

FROM THE AUTHORS' CONCLUSIONS. (WARREN C. HUNTER.)

THE THYMUS AND ADRENALS IN THE RESPONSE OF THE ORGANISM TO INJURIES AND INTOXICATIONS. H. SELYE, Brit. J. Exper. Path. **17**:234, 1936.

In the rat a syndrome consisting of rapid involution of the thymus, formation of a pleural transudate and enlargement of the adrenals with loss of cortical lipoids is produced by certain operative injuries, drugs, low temperatures and stimuli causing merely nervous excitement. In fact, among all the stimuli tried, none has been found which would seriously damage the experimental animal without causing rapid involution of the thymus and enlargement of the adrenals. The involution produced by such means is more pronounced than that which follows withdrawal of all food and water, and therefore it is not due to failure of the animal to eat. All the injuries and drugs which normally cause involution of the thymus are without effect on the size of the thymus of an adrenalectomized animal. In the hypophysectomized rat they have some effect but much less than in the normal rat. A method for removing the adrenal medulla with a suction pump is described. This method allows removal of the medulla without serious injury to the cortex. The thymus of a rat thus deprived of medullary tissue but still in possession of active cortical tissue shows little if any ability to involute. The inability of the

thymus of the adrenalectomized animal to undergo involution is not restored by sodium chloride, extract of adrenal cortex in such doses as have been used, or epinephrine. Sodium chloride heightens the otherwise low resistance of adrenalectomized rats to toxic doses of various drugs if the animals receive food. It is quite inactive, however, in fasting animals. The changes caused by a drug when it is given for the first time will subside later in spite of the continued administration of the drug. It appears, therefore, that the syndrome described, consisting of thymic edema followed by involution, formation of a pleural transudate, enlargement of the adrenal cortex with loss of its lipoid granules, and rapid loss of body weight, represent an "alarm reaction" which enables the organism to meet critical situations more efficiently. Attention is called to the possible connections between these experimental findings and the clinical observations of drug habituation, on the one hand, and nonspecific fever and protein therapy, on the other.

FROM THE AUTHOR'S SUMMARY.

CHANGES INDUCED BY ESTROGENS IN THE ADRENALS OF MALE MICE. H. BURROWS, J. Path. & Bact. **43**:121, 1936.

Characteristic changes in the adrenal gland of the male mouse following prolonged treatment with several pure estrogenic compounds are described. The sequence of changes appears to be (1) the reappearance of the so-called X zone present in the adrenal gland in early life and (2) the production by the cells of this zone of lipoid-like material, which may form relatively large rounded masses that stain poorly, lying in the vascular stroma between the cortex and the medulla.

FROM THE AUTHOR'S SUMMARY.

THE HYPERERGIC REACTION OF THE DENERVATED KIDNEY. H. KAISERLING and W. MATHIES, Virchows Arch. f. path. Anat. **295**:458, 1935.

Rabbits were sensitized by four subcutaneous injections of swine serum, given at five day intervals. The kidney was denervated by sectioning all the nerves entering the hilus and by stripping the adventitia of the renal artery, or by extirpation of both celiac ganglions together with the renal ganglion of one side and sectioning the splanchnic nerves and the branches of the sympathetic trunk and of the nerves entering the hilus of the kidney. Denervation in the sensitized animal led to paralytic hyperemia of the glomerular and intertubular capillaries, the process reaching its height in from twenty-four to thirty-six hours. Injection of the activating dose of the antigen directly into the renal artery of the denervated kidney led to intensification and more rapid development and progress of the hyperergic inflammatory reaction. Injection of the antigen into the general circulation led to a local allergic reaction in the denervated kidney. Stasis and the slowing of the capillary circulation brought about by denervation furnish an anatomic background for the more intense allergic reaction, in that the antigen acts for a longer time on the sensitized tissues. Nervous regulation through an intact nervous system is of the greatest significance in the development of the hyperergic reaction. Disturbance of such normal regulation may be an important factor in clinical allergic states.

O. T. SCHULTZ.

LUNG TISSUE CULTURE. W. SCHOPPER, Virchows Arch. f. path. Anat. **295**:623, 1935.

The controversial question of the existence or nonexistence of pulmonary alveolar epithelium and of the origin of the alveolar phagocytes was subjected to investigation by the method of tissue culture. In cultures of embryonic guinea-pig lung the epithelium of the primitive air vesicles could be readily distinguished from the mesenchyme. This difference was evident in the actively growing tissue. In cultures of the lungs of young guinea-pigs there was active outwandering of histiocytic macrophages, which were not of hematogenous origin. On morphologic

grounds it was not possible to determine the epithelial or mesenchymal origin of the rounded cells free within the alveoli. The ciliary activity of the epithelium of the larger bronchi and of the trachea persisted for weeks. The ciliated epithelium grew in the form of membranes, in which ciliary activity was retained. Ciliary activity was resistant to many factors that influenced the culture adversely. In cultures of embryonic chick and guinea-pig lung the smooth muscle of the small and growing bronchi exhibited autonomic contractility, often in spiral or peristaltic fashion.

O. T SCHULTZ.

Pathologic Anatomy

PERICARDIAL LESIONS IN RHEUMATIC FEVER. C. K. FRIEDBERG and L. GROSS, Am. J. Path. **12**:183, 1936.

Friedberg and Gross describe the gross and microscopic pericardial lesions found in eighty-seven persons with active and inactive rheumatic fever. These patients were divided into five clinical groups depending on the course of the disease. It is shown that while in each group the lesions may present individual differences, as a whole they fall into three more or less characteristic histologic patterns. The data presented on the incidence of the various lesions show rheumatic disease of the heart almost invariably associated with certain inflammatory changes in the pericardium. A description is given of the histologic changes in the normal pericardium with age.

FROM THE AUTHORS' SUMMARY.

NUCLEAR ALTERATIONS FOLLOWING INTRAVENOUS INJECTIONS OF GLUCOSE AND OF OTHER SOLUTIONS. J. LEE, Am. J. Path. **12**:217, 1936.

Nuclear changes were produced (1) by intravenous injection of a hypertonic solution of dextrose, of dextrose plus acacia, of sodium chloride or of sodium bicarbonate and (2) by injection of a large quantity of distilled water. With injections of the first type changes were noted in the Purkinje cells of the cerebellum, anterior horns of the spinal cord, spinal and sympathetic ganglions and the pyramidal cells throughout the thickness of the cerebral cortex; with injections of the second type changes appeared in cells of the anterior horns of the spinal cord and the spinal ganglions. No nuclear alterations were noted in any other tissues examined. The nuclear reactions produced by the hypertonic solutions resembled the early alterations in nerve cells following pseudorabies, herpes and B virus infection, while those produced by distilled water more closely resembled the inclusions observed in poliomyelitis and Borna disease; but it was not possible to produce any nuclear inclusions which were so much like the inclusions observed in virus diseases that they could be mistaken for them.

FROM THE AUTHOR'S SUMMARY.

THE PATHOGENESIS OF ACUTE HAEMORRHAGIC PANCREATITIS. A. R. RICH and G. L. DUFF, Bull. Johns Hopkins Hosp. **58**:212, 1936.

In human and experimental hemorrhagic pancreatitis there occurs a constant and specific vascular lesion, characterized by rapid necrosis of the walls of arteries and veins. The pancreatic hemorrhage results from the rupture of the necrotic vessels. This vascular necrosis is the direct result of the action of pancreatic juice on the walls of the vessels, and the agent in the juice responsible for the necrosis is the tryptic ferment. A precisely similar lesion can be produced in vessels elsewhere in the body by injecting locally purified trypsin or pancreatic juice obtained from the duct through a cannula. Activation of trypsinogen by enterokinase is not necessary for the production of the vascular necrosis. Inactivation of trypsin by heat destroys its necrotizing power. Aside from the rare instances of primary rupture or occlusion of the pancreatic blood vessels, hemor-

rhagic pancreatitis occurs only as a result of disruption of the duct-acinus system, with consequent escape of the secretion into the interstitial tissue of the gland. In the majority of cases hemorrhagic pancreatitis results from partial obstruction to the outflow of the secretion, causing distention and rupture of acini and ductules behind the obstruction, with resulting escape of pancreatic juice into the interstitial tissue. If the escaping juice is rich in tryptic ferment and comes into contact with arteries and veins, their walls will be destroyed, and extensive or localized hemorrhage will occur, depending on the size of the affected vessels. If no arteries or veins are present in the vicinity of the acinar rupture, or if the escaping secretion has low tryptic power, fat necrosis, produced by the lipase of the juice, may be the only result. Rupture of dilated, thinned-out acini behind an obstruction is particularly liable to occur during the periods of increased pressure within the system resulting from stimuli which greatly increase the production of secretion (e. g., a large meal or the ingestion of alcohol). While the underlying obstruction in some cases of hemorrhagic pancreatitis is caused by a gallstone lodged at or near the ampulla of Vater, in most cases the main pancreatic duct is unobstructed, and the obstruction is situated in branches of the duct within the pancreas. Retrojection of bile into the pancreatic duct is an infrequent cause of hemorrhagic pancreatitis in the authors' experience, and reports of cases proved to be of this sort are scarce in the literature. Even in the cases in which retrojection of bile occurs, hemorrhagic pancreatitis does not result unless the duct-acinus system is ruptured and a secretion with sufficient tryptic potency to produce vascular necrosis escapes. Metaplasia of the epithelium of the branches of the pancreatic duct, leading to partial obstruction and consequent distention of the acini and ductules behind the obstruction, is a very frequent occurrence, having been found in the authors' routine sections in 18.6 per cent of 150 consecutive autopsies on persons over 25 years of age. Rupture of the distended acini behind the obstructing metaplasia also occurs frequently, but in most cases the resulting damage is limited to focal fat necrosis or small hemorrhages. There is evidence that acute attacks of severe epigastric pain may be associated with these accidents. Metaplasia of duct epithelium with associated acinar distention was found in the routine sections in thirteen of twenty-four cases of hemorrhagic pancreatitis. It is believed that this form of obstruction leading to acinar rupture and escape of secretion plays an important rôle in the pathogenesis of many cases of hemorrhagic pancreatitis, though any of the numerous causes of duct obstruction may, of course, lead to the same result.

FROM THE AUTHORS' SUMMARY.

UNILATERAL TRAUMATIC SELECTIVE DEGENERATION OF THE PALLIDUM AND STRIATUM. W. G. SPILLER, Arch. Neurol. & Psychiat. **35**:310, 1936.

In Spiller's patient a left pallidostriatal and subthalamic lesion followed an injury to the head from a fall. The patient recovered completely, but about four years later he presented pallidostriatal signs—tonic spasms of the toes of the foot and numbness in the right hand with hyperextension of the fingers. Nine years after the injury he began to experience "minor psychic attacks," which two years later were accompanied by unconsciousness, difficulties of speech, loss of memory and irritability. Contracture of the right foot developed with slight spastic paralysis and sensory disturbances in the right leg and, to some degree, in the right arm (loss of vibration sense) and the right side of the face. Necropsy revealed a scar in the pallidum and putamen and in the knee of the left internal capsule. The left nucleus caudatus was destroyed; the corresponding horn of the lateral ventricle was dilated. In the inner portion of the left paracentral lobule there was an accumulation of granules of hemosiderin around a blood vessel—remnants of an old hemorrhage that had occurred eighteen years previously. No changes were found in the paracentral cortex, optic thalami, red nuclei, right cerebellar cortex or pyramidal tract, but the corresponding corpus subthalamicum was destroyed, and in the left substantia nigra there was much loss of cells in the zona reticulata.

G. B. HASSIN.

THE PATHOLOGY OF SYNOVIAL EFFUSIONS. D. H. COLLINS, J. Path. & Bact. **42**: 113, 1936.

The extent to which inflammatory exudation contributes to the formation of an effusion can be determined by cytologic examination of the fluid. The two most important estimations are the total cell count and the differential polymorphonuclear count. The difference in the cell values of the fluid in osteo-arthritis of traumatic origin and the fluid in arthritis of rheumatoid type is very striking and reflects the difference in the underlying pathology. The importance of the cytologic examination is further shown by two examples of "sympathetic" effusion, the result of acute inflammatory lesions near the joint. In neither was there a significant abnormality of the total cell or polymorphonuclear count and in neither were the joint tissues themselves involved in the inflammatory process.

FROM THE AUTHOR'S CONCLUSIONS.

BRONCHIECTASIS AND METAPLASIA IN THE LUNG OF THE RAT. R. D. PASSEY, A. LEESE and J. C. KNOX, J. Path. & Bact. **42**:425, 1936.

The common bronchiectasis of the laboratory rat is described. Metaplasia in bronchiectatic cavities is described, and the keratinization of the metaplastic epithelium is correlated with a deficiency of vitamin A. Extreme squamous metaplasia in the lung of the rat is compared with lesions erroneously reported by previous workers as primary or secondary squamous carcinoma.

FROM THE AUTHORS' SUMMARY.

NECROSIS WITH CALCIFICATION OF THE ADRENAL GLANDS. R. GOLDSTEIN, Frankfurt. Ztschr. f. Path. **47**:360, 1935.

An instance of endocarditis associated with necrosis and calcification of the adrenal glands is reported. The patient had pain in the back, moderate elevation of the temperature and a gradual lowering of the arterial blood pressure. Autopsy revealed an acute verrucous endocarditis of the mitral valve together with acute fibrinous pleuritis, pericarditis and peritonitis. The right adrenal gland was swollen, brownish red and surrounded by a small rim of cortical tissue. In an area measuring 0.75 by 2 cm. in diameter the medulla was replaced by a grayish-yellow, apparently necrotic tissue containing dark red dots. Similar changes were also found in the left adrenal gland. Microscopic examination revealed recent thrombi in a number of small blood vessels with large areas of necrosis and a number of bluish-stained amorphous concrements which gave the histochemical reactions of calcium.

OTTO SAPHIR.

COLLAGEN AND RETICULUM FIBERS IN NECROTIC FOCI. S. F. LOPEZ, Frankfurt. Ztschr. f. Path. **47**:382, 1935.

Lopez found that collagen as well as reticulum fibers are preserved in necrotic foci of varied etiology in various organs. In the presence of a suppurative process the collagen and reticulum fibers are damaged. Collagen and reticulum fibers play some rôle in the formation of scars. The amount and arrangement of the fibers in the caseous zones of tubercles depend on the conditions previous to the caseation. The differences in reticular structure between a tubercle and a gumma may be so marked as to have diagnostic value in distinguishing the one from the other. Not only lack of necrosis but a very marked proliferation of the reticulum is noted in gummas, in contrast to tubercles, which contain only a previously formed organoid reticulum. Lopez concludes that the common primary causative factor in necrosis is the suppression of the blood supply. The variety of necrosis depends on the slowness or suddenness of the suppression.

OTTO SAPHIR.

GLYCOGEN DISEASE. V. FABER, Frankfurt. Ztschr. f. Path. **47**:443, 1935.

An infant with a hard and distended abdomen died at the age of 1 month. Besides bronchopneumonia, there was found a very large liver weighing 425 Gm.,

or more than one sixth of the body weight (2,400 Gm.). The size of the liver was due to extensive glycogen deposits in the parenchyma. Glycogen deposits were present in the kidney epithelium. There also was chronic pancreatitis, which was diagnosed microscopically. The number of the islands of Langerhans was apparently reduced. Irregularities in the size and shape of the islands were also observed. Chemical examination revealed a glycogen content of 15.3 per cent in the liver and 5.9 per cent in the kidney. Faber believes that primary changes of the pancreas are responsible for this disease.

OTTO SAPHIR.

TRANSVERSE INTIMAL STRIATION OF THE ARTERIAL SYSTEM. J. LEWIN, Virchows Arch. f. path. Anat. **295**:39, 1935.

Lewin in 1933 described (Abstr., ARCH. PATH. **16**:881, 1933) the frequent occurrence of transverse ridges or striations of the inner surface of the brachial artery. He concluded that they resulted from the healing of ruptures of fibrils of the internal elastic membrane. The striations are seen only in the arteries of muscular type. The present report is based on a study of the various arteries of twenty-five persons aged from 16 to 60 years. Transverse striation of the intima is of almost universal occurrence and begins early in life, the striations increasing in number with advancing age. They are most numerous in the arteries of the lower extremity, next in those of the upper extremity, then in the branches of the abdominal aorta and in the arteries of the neck. Of the abdominal arteries, the splenic is most markedly involved. In forty-five necropsies of persons aged from 16 to 22 years especial attention was paid to the coronary arteries. Because of the thickness of the walls of these arteries the striations are less evident, but tears of the internal elastic membrane were observed in thirty-two of the hearts examined. Tortuosity of the coronary arteries is the result not of this process, as some have claimed, but of myocardial atrophy and loss of elasticity of the vessels. Rupture of elastic fibrils with intimal striation, in whatever muscular artery the process may occur, is the result of mechanical factors.

O. T. SCHULTZ.

THE ENDOCRINE SYSTEM IN OSTEOGENESIS IMPERFECTA. L. THER, Virchows Arch. f. path. Anat. **295**:57, 1935.

A number of writers have held that osteogenesis imperfecta is the result of abnormality of the endocrine system. Ther reports a case in a girl aged 6 years who at the time of death presented no abnormality of any of the endocrine organs. In a brief appendix he reports a second case in a child aged 3 months in whom also there were no detectable endocrine abnormalities.

O. T. SCHULTZ.

EDEMA OF THE SPLEEN. K. HELMKE, Virchows Arch. f. path. Anat. **295**:86, 1935.

Edema of the spleen has been rarely described, and there is some question as to its occurrence. In the spleen of a person who died of hemorrhage Rössle noted a histologic picture which he interpreted as indicative of parenchymatous edema. The work reported here, done in Rössle's laboratory, is based on an examination of ninety spleens from persons with various disease processes. The water content was determined by drying, the blood content by estimation of the hemoglobin, and the results of these determinations were correlated with the histologic picture. The blood and water contents were found to bear an inverse relation to each other. High water content was noted in the spleen in hemorrhage and infectious diseases and in the generalized hydrops of cardiac decompensation and nephrosclerosis. The blood content of the spleen in hemorrhage and infection is relatively low; this is ascribed to terminal contraction of the spleen. The histologic changes of parenchymatous edema of the spleen, which is due to escape of fluid from the capillaries of the pulp and follicles, are described. In children there appears to be a barrier to the ready passage of fluid from the capillaries of the follicle to the

surrounding pulp; to this is ascribed the frequent absence of swelling of the spleen in infectious diseases of children. The edema of hydrops differs from that of infection in that the follicles are better preserved in hydrops.

O. T. SCHULTZ.

TOPOGRAPHIC RELATIONS OF THE PROSTATE IN HERMAPHRODITISM. L. MOSZKOWICZ, Virchows Arch. f. path. Anat. **295**:211, 1935.

In a previous communication the author described the relation of the prostate to the vagina and urethra in hermaphroditism and presented the results of a study of the embryologic development of the prostate. The latter begins its development before any sexual differentiation has occurred. In the male it continues to grow; in the female it disappears. In pseudohermaphroditism with female gonads the prostate lies cephalad to the union of the vagina with the urethra. In pseudohermaphroditism with male gonads the vagina passes through the prostate, and the greater portion of the latter surrounds the urethra caudad to the union of the vagina with the urethra. The study reported here is based on an examination of six further specimens of hermaphroditism, two masculine and four feminine. The previous findings of the relations of the prostate are confirmed. It is of passing interest that one of the specimens had been placed in the museum by Rokitansky in 1848. Knowledge of the relations of the prostate in hermaphroditism and of the normal embryogenesis of the prostate makes it possible to determine when the change from one sex to the other occurred.

O. T. SCHULTZ.

NECROSIS OF ARTERIOSCLEROTIC PLAQUES AND ITS RELATION TO ATHEROMA. P. JUCKER, Virchows Arch. f. path. Anat. **295**:301, 1935.

In Jucker's histologic study of early necrosis in arteriosclerotic plaques of the aorta, necrosis was never observed in young, loosely fibrillated and cellular plaques but only in those that had undergone some sclerosis and hyalinization. Some of the latter were free from necrosis. The earliest stage of necrosis is preceded by edema and degeneration of the ground substance. It was impossible to detect any relationship between necrosis and the size of the plaque or the degree of hyalinization or the intensity of fatty infiltration or the nutritional state of the plaque as determined by the vascularity of the latter. Jucker is therefore led to postulate that necrosis is due to some poison or toxin, which is perhaps soluble in lipoids. Lipoid substances in themselves do not induce necrosis. Necrosis is followed by disintegration of the necrotic tissue and by lipoid and calcium infiltration. The area of atheromatous softening may break through the covering intimal tissue.

O. T. SCHULTZ.

Microbiology and Parasitology

RECOVERY OF A FILTRABLE VIRUS FROM CHILDREN WITH INFLUENZA. I. J. BRIGHTMAN and J. D. TRASK, Am. J. Dis. Child. **52**:67 and 78, 1936.

During the influenza epidemic of 1934-1935, an agent capable of infecting ferrets could readily be recovered from the nasopharyngeal washings of children ill with the disease. The findings reported corroborate the earlier findings of Smith, Andrewes and Laidlaw and of Francis. The infective agent was a filtrable virus. The strains of virus recovered in New Haven are immunologically identical with it. The hemolytic streptococcus, originating in the ferret, became prominent on serial passage of the influenza virus.

FROM THE AUTHORS' SUMMARIES.

EPIZOOTIC ENCEPHALITIS IN FOXES. R. G. GREEN and others, Am. J. Hyg. **24**:57, 1936.

These studies establish that epizootic encephalitis can be produced in foxes by way of the upper respiratory tract. It is shown that the virus in the upper respiratory tract can be identified by injecting filtered nasal washings into foxes.

Using this technic, the authors studied the natural spread of the disease in a group of red foxes. Following the initial spread of the infection, a second spread was occasioned by artificially increased contact. Subsequent to a closed serum-virus injection, the virus appeared in the upper respiratory tract of only those animals in which infections developed after a delay. All studies seemed to show a high affinity of the virus for the upper respiratory tract. The specific inclusions were demonstrated in cells associated with the surface epithelium of the upper respiratory tract. In definite ulcers nearly all the cells contained the inclusions. It seems evident that the upper respiratory tract is the portal of entry for the virus, and that the virus gains entrance by direct involvement of the surface cells. The development of virus in the upper respiratory tract after a closed intramuscular injection of the virus appears to be due to the involvement of surface epithelium as a part of the general infection. It is indicated that persistence of the virus in the surface cells of the upper respiratory tract is responsible for the carrier state which has been obvious in epidemiological studies.

FROM THE AUTHORS' SUMMARY.

RECOVERY OF INFLUENZA VIRUS SUSPENDED IN AIR AND ITS DESTRUCTION BY ULTRAVIOLET RADIATION. W. F. WELLS and H. W. BROWN, Am. J. Hyg. **24**:407, 1936.

The virus of influenza was recovered after being suspended in air for at least thirty minutes. The infectivity of the P. R. 8 strain for ferrets was destroyed by ultraviolet radiation.

FROM THE AUTHORS' SUMMARY.

THE GORDON TEST FOR HODGKIN'S DISEASE. JACOB D. GOLDSTEIN, Am. J. M. Sc. **191**:775, 1936.

In seven of nine cases of Hodgkin's disease biopsy material produced an encephalitic syndrome (a positive Gordon test) when inoculated intracerebrally into rabbits. Twenty control lymph nodes, including five tuberculous nodes and two nodes showing infectious mononucleosis, yielded negative results. No tests were falsely positive. Two of nine nodes in cases established to be instances of Hodgkin's disease failed to give positive results.

FROM THE AUTHOR'S SUMMARY.

A VIRUS DISEASE OF OWLS. R. G. GREEN and J. E. SHILLINGER, Am. J. Path. **12**:405, 1936.

A virus disease has been recognized as a disease of the great horned owl (Bubo virginianus). It has been transmitted experimentally to the same species and to the screech owl (Otus asio) but not to the barred owl (Strix varia varia). It is characterized by the formation of multiple abscesses in the liver and, less consistently, in the spleen. Large intranuclear inclusions occur typically in the hepatic cells.

FROM THE AUTHORS' SUMMARY.

NEUROTESTICULAR AND DERMAL STRAINS OF VACCINE VIRUS IN THE CHORIO-ALLANTOIC MEMBRANE OF THE CHICK EMBRYO. G. J. BUDDINGH, Am. J. Path. **12**:511, 1936.

A neurotesticular strain of vaccine virus produces a hemorrhagic lesion in the chorio-allantoic membrane of the chick embryo and in the rabbit's skin. The hemorrhagic character of the lesion produced by the neurotesticular vaccine has been maintained through fifty passages in serial transfer in the membranes of chick embryos. A comparative histologic study of the lesions produced by a dermal and a neurotesticular strain of vaccine virus in the membranes of chick embryos and in the skins of rabbits has shown that the neurotesticular strain is characterized by a special affinity for mesodermal structures, especially the endothelial cells

of the blood vessels. During cultivation in the chorio-allantoic membrane the characteristic qualities of a particular strain of vaccine virus are preserved apparently indefinitely.

FROM THE AUTHOR'S SUMMARY.

CULTIVATION OF TUBERCLE BACILLI FROM THE BLOOD. M. SIEGEL and B. SINGER, Am. Rev. Tuberc. **32**:563, 1935.

The Löwenstein method of cultivating tubercle bacilli from the blood was employed for 911 specimens from 422 living tuberculous persons. There were 6 (1.4 per cent) macroscopically positive cultures and 55 (13 per cent) microscopically positive cultures. The macroscopic cultures were undoubtedly cultures of tubercle bacilli, according to subculture and virulence tests. The microscopic cultures were not definitely proved to be cultures of tubercle bacilli, since subcultures and animal inoculations gave negative results. The primary macroscopic growths were scant, usually only one or two colonies appearing from a sample of from 5 to 10 cc. of blood. The six macroscopically positive cultures were obtained from the following: a couple of infants with miliary tuberculosis, an adult critically ill with pulmonary and intestinal tuberculosis, an adult immediately after a first stage thoracoplasty operation, the umbilical blood of a tuberculous placenta, and the postmortem cardiac blood of a new-born infant who died three hours after birth with no evidence of tuberculous lesions. Hemoglobin did not seem to inhibit the growth of tubercle bacilli, according to a comparative study of the Löwenstein method and the "whole blood" method. In this series of 98 specimens from 63 tuberculous persons, there were 3 macroscopically positive cultures by the direct culture of whole citrated blood as compared with 2 macroscopically positive cultures and 1 microscopically positive culture by the use of Löwenstein's method.

FROM THE AUTHORS' SUMMARY.

THE VIRUS OF PEMPHIGUS AND HERPETIFORM DERMATITIS. E. URBACH and S. WOLFRAM, Arch. Dermat. & Syph. **33**:788, 1936.

Rabbits inoculated with the blood serum and the fluid from blisters of patients with pemphigus vulgaris and herpetiform dermatitis exhibited a characteristic clinical and anatomic picture. A similar disease was manifested by animals given injections of filtrates of the skin, mucous membranes, spleens and lymph nodes removed at autopsy from patients who had died of pemphigus. Attempts at transmission of the infection from human beings to animals and its passage through animals were repeatedly successful. The numerous successful transfers made with filtrates of fluid from blisters, blood serum and brain tissue point to an invisible filtrable virus as the cause of these diseases. The blood serum of patients with pemphigus contains antibodies specific for the antigen present in the blisters of patients as well as in the brains of infected animals. Animal inoculations and serologic tests are therefore of diagnostic importance. Immunologic investigations demonstrate that cross-immunity between the viruses of pemphigus and herpes does not exist. Animals which have recovered from pemphigus are immune to reinfection. Some animals appear to have been silently immunized. These experiments indicate that pemphigus vulgaris and herpetiform dermatitis are caused by one and the same virus. They represent different forms of the same disease.

FROM THE AUTHORS' SUMMARY.

CULTIVATION OF THE VIRUS OF LYMPHOGRANULOMA VENEREUM IN MICE. A. W. GRACE and F. H. SUSKIND, Arch. Dermat. & Syph. **33**:853, 1936.

A strain of the virus of lymphogranuloma venereum obtained from the pus and glandular material of a patient presenting the inguinal type of the disease has been successively transmitted in mice by intracerebral inoculation for forty-one passages. The virus increased in virulence with successive passages in mice. Lymphogranulomatous mouse brains provided a readily available source of specific Frei antigen, the potency of which increased with successive passages. Frei antigens

prepared from mouse brains were tested six months after preparation and found to retain their potency for at least that length of time. Emulsions of normal mouse brains prepared and tested in the same way as Frei antigen did not produce any appreciable reaction. In 143 Frei tests done on twenty-two lymphogranulomatous human subjects and the 145 tests done on thirty-eight normal human subjects, no untoward effects were caused by the use of material prepared from mouse brains. The brains of mice which died after an intracerebral inoculation of the virus of lymphogranuloma venereum showed meningo-encephalitis on histologic examination. Exudation into the meninges and ventricular system and perivascular infiltration with infrequent formation of abscesses in the brain substance were the chief pathologic observations. The inflammatory cells were polymorphonuclear leukocytes, macrophages, plasmacytoid cells, small lymphocytes (a few) and very large cells, possibly macrophages. The proportions in which the cells of the first three types occurred depended on the length of time that had elapsed between inoculation and death. Intracytoplasmic bodies were encountered infrequently.

FROM THE AUTHORS' SUMMARY.

EXPERIMENTAL PRODUCTION OF WHOOPING COUGH IN CHIMPANZEES. A. R. RICH and others, Bull. Johns Hopkins Hosp. **58**:286, 1936.

A condition similar in all respects to whooping cough, i. e., characterized by coryza followed by a protracted paroxysmal cough typical of that of pertussis and associated with lymphocytosis and the development of positive complement fixation toward the Bordet-Gengou bacillus, has been produced in the chimpanzee by oral administration of unfiltered tracheal exudate of patients with pertussis. Bordet-Gengou bacilli were recovered on cough plates at the height of the cough. A precisely similar condition has been produced in the chimpanzee by oral administration of pure cultures of Bordet-Gengou bacilli. It is therefore clear that the characteristic clinical features of pertussis can be produced in apes by these bacilli acting alone. The inoculation of apes with bacteriologically sterile blood and filtered respiratory secretions obtained from four patients with pertussis early in the disease was followed by the appearance of catarrh of the upper respiratory tract without cough. In the one instance in which an attempt was made to transfer the agent from one ape to another by means of a bacteriologically sterile filtrate of the nasopharyngeal secretions, the attempt was successful. The nature of this filtrable agent is discussed. Its relation to pertussis is undetermined. At present one can say only that the Bordet-Gengou bacillus acting alone is capable of producing the characteristic clinical manifestations of whooping cough in the ape.

FROM THE AUTHORS' SUMMARY.

INTESTINAL FLORA OF CHICKENS AFFECTED WITH ENTERITIS AND INTESTINAL PARASITISM. W. W. EMMEL, Florida Agric. Exper. Stat., Tech. Bull. 293, 1936.

In chickens intestinal parasitism is associated with grave changes in the normal flora, in the course of which bacteria of the typhoid and paratyphoid groups may become established in the intestine. Chickens consequently may offer a source for the spread of typhoid and paratyphoid bacteria.

FROM THE AUTHOR'S SUMMARY.

THE OLFACTORY BULBS IN EXPERIMENTAL POLIOMYELITIS. A. B. SABIN and P. K. OLITSKY, J. A. M. A. **108**:20, 1937.

The virus of poliomyelitis produces characteristic lesions in the olfactory bulbs of rhesus monkeys when it invades the central nervous system by way of the olfactory nerves. These lesions are absent when the invasion of the central nervous system is by other pathways. Postmortem examination of the olfactory bulbs may therefore serve to indicate the portal of entry of the virus under natural conditions.

FROM THE AUTHORS' SUMMARY.

AN EPIDEMIC IN A MOUSE COLONY DUE TO THE VIRUS OF ACUTE LYMPHOCYTIC CHORIOMENINGITIS. E. TRAUB, J. Exper. Med. **63**:533, 1936.

A filtrable virus identical with that which causes acute lymphocytic choriomeningitis has been found to cause a disease in white mice. Naturally infected mice usually show no symptoms, but such animals inoculated intracerebrally with sterile bouillon or other materials present characteristic symptoms. The same symptoms are produced by intracerebral injection of the virus into mice from a disease-free stock. Guinea-pigs are very susceptible and are therefore useful for detecting the virus and for neutralization tests. The disease as studied in both naturally infected and inoculated animals is discussed, and the pathologic observations are given.

FROM THE AUTHOR'S SUMMARY.

THE COMMON COLD. A. R. DOCHEZ, K. C. MILLS and YALE KNEELAND JR., J. Exper. Med. **63**:559, 1936.

Detailed descriptions are given of the methods employed to isolate the virus of the common cold, to preserve and cultivate it and to test its activity in human volunteers. The virus can be isolated easily from properly selected patients and cultivated in a tissue medium. When kept in the original nasopharyngeal washings it will survive at icebox temperature under anaerobic conditions for at least thirteen days. If the nasopharyngeal washings are frozen and dried in vacuo the virus retains its activity for at least four months. It has been proved to multiply in a medium containing chick embryo. Cultures in such a medium retain their capacity to produce the typical infection in human beings through many transfers involving a period of several months. Attempts to cultivate the virus have been successful in seven of eight instances. Prolonged cultivation in a tissue medium eventually leads to loss of activity. Strains under cultivation maintain their potency best when transfers are made at two and three day intervals. After removal from the incubator a culture of the virus rapidly becomes inactive whether it is kept under seal in the icebox or frozen and dried in vacuo. The destructive action of the medium can be prevented if the culture is mixed with acacia before freezing and drying in vacuo.

FROM THE AUTHORS' SUMMARY.

CYTOPLASMIC INCLUSION BODIES IN THE HUMAN THROAT. J. BROADHURST, R. M. LIMING and M. E. MACLEAN, J. Infect. Dis. **58**:134, 1936.

Cytoplasmic inclusion bodies may be demonstrated in the human throat and other parts of the upper respiratory area. A relatively high proportion of persons with certain of the milder respiratory irritations carry these inclusion bodies. The carriers may show an increasingly heavy incidence in the epithelial cells of the throat—both as to the number of cells affected and as to the number of bodies per cell. The inclusion bodies are rarely present in epithelial cells which contain bacteria. They are easily demonstrated in the epithelial cells of affected persons, but they do not persist, in the same form at least, outside the host cells.

The epithelial inclusions seem acceptably classified as inclusion bodies: They multiply only when living tissue is available. They stain pink with Giemsa's stain (after fixation in Zenker's fluid). An aggregate structure (as in the Negri bodies of rabies) and a capsule may be demonstrated by appropriate stains. Special stains have been developed for their ready differentiation from other cell parts and constituents and extraneous material: notably a nigrosin-sodium chloride preparation for throat specimens and a methyl green-pyronine stain for embryo chick cultures. Cytoplasmic inclusion bodies have been cultivated in throats of monkeys and in embryo chick tissues.

FROM THE AUTHORS' SUMMARY.

VARIATION OF SALMONELLA PULLORUM. H. VAN ROEKEL and L. F. RETTGER, J. Infect. Dis. **58**:172, 1936.

Among 163 freshly isolated strains of Salmonella pullorum, 13 variants were detected. The behavior of these variants in sodium chloride solution of different

concentrations and in the presence of positive and negative serums differed greatly. Other properties, such as colonial and cellular morphology, Gram-staining and biochemical reactions revealed on the whole little or no variation. Strains of S. pullorum readily underwent variation when subjected to frequent transfer and storage in beef infusion broth. When variants were cultivated on both meat extract agar and liver infusion agar the colonial and cellular features often appeared markedly different. Some strains that appeared normal on meat extract agar exhibited pleomorphic tendencies when placed on liver infusion agar.

Most variants exhibited a lesser degree of virulence than their parent strains and in some instances appeared avirulent. The agglutinogenic power and the absorptive capacity of the variants tested were not equal to those of the normal type.

FROM THE AUTHORS' SUMMARY.

STREPTOCOCCI OF SUBACUTE BACTERIAL ENDOCARDITIS. H. FOX, J. Infect. Dis. **58**:230, 1936.

The data presented seem to suggest that there is a relationship between the clinical character of subacute bacterial endocarditis and the biologic criteria accepted by Lancefield as indicative of the human origin of certain streptococci. They also indicate that there is a direct relationship of the rough character of colonies on the mediums used in this study to the violence of the morbid process. They suggest that slower development of subacute bacterial endocarditis is associated with streptococci from a nonhuman source and relatively more often smooth originally or throughout. They seem to indicate that pathogenicity for mice may be found more often than is customarily reported.

This study fits in with that reported by Tunnicliff and Woolsey and complements their work by adding the thought of the relativity of clinical and bacteriologic findings. It adds to some extent to the assumption of Rosenow discussed in the report just cited, which would give considerable significance to rough colonies. Finally it appears to assign to rough streptococci, which are usually accredited with an invasiveness less than that of smooth streptococci, a special importance perhaps high enough for the bacteriologist to report them to the clinician and for the latter to evaluate them as significant in the interpretation of his clinical case.

FROM THE AUTHOR'S SUMMARY.

Immunology

THE ANTIGENIC FUNCTION OF THE KIDNEY. F. HAHN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **86**:31, 1935.

Hahn undertook this investigation on account of the conflict in the results of previous investigations. The discrepancies proved to be due to the difference in the antigenic properties of kidney tissue in different species. While the kidney of the ox produced only occasionally an antiserum with very slight organ specificity, the kidney of the rat produced regularly such organ-specific immune serum, which had, in addition, specific antibodies against the lipoids of the kidney.

I. DAVIDSOHN.

HYPERSENSITIVENESS OF GUINEA-PIGS TO ARSPHENAMINE. R. LAUF, Ztschr. f. Immunitätsforsch. u. exper. Therap. **86**:49, 1935.

Guinea-pigs were given repeated intracutaneous injections of small doses (from 0.01 to 0.1 mg.) of neoarsphenamine, and after varying intervals they received intracardiac injections of from 6 to 15 mg. of the same drug. A large number of them reacted with moderate to marked anaphylactic symptoms, but all survived. The results prove that arsphenamine is a full antigen. The optimum interval for the development of hypersensitiveness was six months after the sensitizing injections, and these were more effective when given in repetition. The total quantity

of the drug administered for sensitization was not important. The type of food that was given during the winter and the drop in atmospheric pressure favored more intensive anaphylactic symptoms.

I. DAVIDSOHN.

ACTIVE IMMUNIZATION OF THE CENTRAL NERVOUS SYSTEM AGAINST TETANUS. A. W. PONOMAREW and W. A. PEROTTI, Ztschr. f. Immunitätsforsch. u. exper. Therap. **86**:65, 1935.

Subcutaneous and intravenous inoculations of tetanus anatoxin did not protect rabbits against intracerebral or subarachnoid injections of the toxin, but very efficient protection, with production of large quantities of antitoxin, resulted from subarachnoid inoculations of the anatoxin. The antibody is produced locally in the central nervous system. The development of antibodies in the blood is also more rapid and more intensive following subarachnoid than after subcutaneous or intravenous inoculation. The results in dogs were essentially similar to those in rabbits.

I. DAVIDSOHN.

EFFECT OF RETICULO-ENDOTHELIAL BLOCKADE ON VACCINATION. O. MÜNDEL and S. ZURUKZOGLU, Ztschr. f. Immunitätsforsch. u. exper. Therap. **86**:87, 1935.

Among the different attempts to explain the origin of postvaccinal encephalitis, that of van Bogaert was based on the genetic relation between the skin and the central nervous system. When the former fails in its function, the blood-cerebrospinal fluid barrier breaks down, and invasion of the central nervous system results. H. Schmid reported experimental confirmation of this hypothesis by blocking the reticulo-endothelial system of the rabbit with acriflavine hydrochloride and finding after subsequent vaccination a very insignificant cutaneous reaction and the development of encephalitis with positive anatomic findings. Mündel and Zurukzoglu repeated the experiments of Schmid but failed to observe encephalitis. They did note a more rapid development of the cutaneous lesion, its lessened intensity and quicker disappearance as well as an earlier appearance and a lower titer of virucidal substances in the blood as compared with normal controls.

I. DAVIDSOHN.

THE BLOOD GROUP FERMENT IN SALIVA. O. SIEVERS, Ztschr. f. Immunitätsforsch. u. exper. Therap. **86**:130, 1935.

The ferment that has the ability to destroy the blood group substance was shown previously to multiply in broth. The broth retains the destructive property for at least a month if it is kept for the first twenty-four hours in the incubator at 37 C. and after that at room temperature. The ferment is destroyed if kept in the incubator for a few days. During the first few days of standing at room temperature the ferment in the broth can be transplanted to a new broth, but later the transplant ability is lost, although the destructive action against the blood group substance is not affected. The ferment appears to be the product of a multiplying agent. Addition of chloroform in proper concentration prevents the growth of the ferment, but does not interfere with its action. None of various anaerobic bacteria that were isolated from the mouth influenced the blood group substance, but a mixture of all anaerobic bacteria acted like the ferment; i. e., it destroyed the A substance in Witte peptone. The results favor the concept of a multiplication of the ferment substance which destroys the blood group outside and independently of the body.

I. DAVIDSOHN.

LOCAL IMMUNIZATION AGAINST INFECTIONS OF THE SKIN WITH STAPHYLOCOCCI. F. KLOPSTOCK, Ztschr. f. Immunitätsforsch. u. exper. Therap. **86**:213, 1935.

Cutaneous inunctions of staphylococcic vaccines into rabbits were followed after proper intervals by intracutaneous injections of the bacteria, with only slight

and irregular evidence of protection. Application of the bacterial suspension in the form of an ointment immediately after the injection of the bacteria into the skin failed to show any influence on the course of the infection.

I. DAVIDSOHN.

SERODIAGNOSIS OF UNDULANT FEVER. W. MOHR, Ztschr. f. Immunitätsforsch. u. exper. Therap. **86**:235, 1935.

Strains of Brucella abortus with tendencies toward dissociation to R forms showed nonspecific weak agglutination with a small number of normal serums and more marked and more frequent nonspecific agglutination with serums of pregnant women, patients with tuberculosis and patients with various other febrile diseases. The use of reliable S strains as antigens for agglutination tests is strongly recommended. The best test for eliminating the improper spontaneously agglutinating strains is a 0.2 per cent solution of acriflavine.

I. DAVIDSOHN.

Tumors

THE EXPERIMENTAL PRODUCTION OF VISCERAL TUMORS WITH HYDROCARBONS. F. W. ILFELD, Am. J. Cancer **26**:743, 1936.

Cholesterol pellets containing 1, 2, 5, 6-di-benzanthracene, methylcholanthrene or 1, 2-benzpyrene in concentrations of 5 per cent were implanted into the kidney, spleen, liver, uterus, testicle, bone marrow, subperiosteum, stomach or brain in 244 animals. In ten mice and two rats renal epidermoid carcinoma was produced with the pellets containing di-benzanthracene, i. e., in 41.3 per cent of the surviving animals. The incubation period varied from six to ten and one-half months. The renal carcinoma was proved malignant by gross and histologic examination in all cases and by subcutaneous transplantation in four. The tumor of one animal was transplanted through four generations. The transplants had the same histologic features as the parent tumor. The histologic features of the renal cancer indicated its origin from renal pelvic epithelium. The renal histologic changes produced by the pellets before the carcinoma developed are described. The production of fibrosarcoma, presumably arising from the spleen, by methylcholanthrene in one animal, uterine epidermoid carcinoma by di-benzanthracene in one animal, and tumor of the liver by di-benzanthracene in two animals is also described.

FROM THE AUTHOR'S SUMMARY.

THE PRODUCTION OF CANCER BY HYDROCARBONS OTHER THAN THOSE OF THE PHENANTHRENE TYPE. A. A. MORTON, C. F. BRANCH and D. B. CLAPP, Am. J. Cancer **26**:754, 1936.

Morton, Branch and Clapp state that as a result of their work it is now possible to dispense with the two broader requirements for a carcinogenic hydrocarbon. There is no need for a condensed ring system of four or five rings nor for a phenanthrene nucleus. Indeed, there is scant resemblance between the polynuclear noncondensed systems studied by them and the condensed structures discovered earlier. The wide differences in carbon framework which exist can be seen by reference to condensed compounds containing a phenanthrene nucleus and ring and to substances possessing no benzene ring directly attached to another ring. One and only one structural similarity is evident between these three diverse patterns. All have at least four benzene rings. Since benzene has never been shown to produce cancer one might conclude that four rings must be present or that a single ring must be modified in some manner by adjacent rings or groups. Successful as have been their results to date, they are by no means prepared to say that the selection of carcinogenic agents must be made on a basis of chemical reactivity. It is obvious, however, that if carcinogenic activity from various types of hydrocarbons is to be related to any common factor, this cannot

be structure. As a matter of fact, they have no assurance that any common denominator can be found among the various agents. They are continuing their tests on compounds selected on a basis of chemical inactivity. Some phenyl homologs of the two newly discovered series are also being tested. Among these are tri-xenylbenzene, tri-naphthalene benzene, hexa-phenylbenzene and hexa-phenylbiphenyl. It is their immediate object in this particular series not only to throw more light on the general nature of organic substances which may cause cancer but also to accelerate the induction of malignant growths in mice.

FROM THE AUTHORS' SUMMARY.

SENSITIVITY OF DIFFERENT SITES OF THE SKIN OF THE MOUSE TO CARCINOGENIC AGENTS. J. M. TWORT and C. C. TWORT, J. Path. & Bact. **42**:303, 1936.

The skin in the interscapular region is usually more sensitive to carcinogenic agents than that covering the sacral or abdominal regions, while the soles are apparently the most resistant. An animal which is sensitive in one area is usually relatively sensitive in another area. When areas of skin of the same animal are compared it is found that an area which is more sensitive to the production of benign tumors is usually but not necessarily more sensitive to the production of malignant tumors. There is evidence to show that a benign tumor per se in one area influences the production of a benign or a malignant tumor elsewhere, but there is some evidence that a malignant tumor produced in one area retards the development of a malignant tumor elsewhere. This may be due to the debilitating effect of the first malignant tumor. Although the average type of tumor varies with different agents, the site of painting appears to have much less effect in determining the type of tumor. The application of carcinogenic agents in one area retards tumor formation in another, the carcinogenic potency being only about one half to two thirds that of the control. The debilitating effect of the agent on the animal is presumably the cause. Previous applications of oleic acid to a given site cause an increase in the carcinogenic potency of the tar when this is applied at the same site. When the tar is applied at a site different from that previously painted with oleic acid the carcinogenic potency falls below that of the control. Again, the lowering effect is presumably due to the general debilitating effect of the oleic acid.

FROM THE AUTHORS' CONCLUSIONS.

THE HISTOGENESIS OF NEURAL TISSUE IN THE TERATOMA. R. A. WILLIS, J. Path. & Bact. **42**:411, 1936.

The genesis of neuro-epithelium in the teratoma has been studied. This tissue takes origin from a simple plastic epithelium which, like primitive embryonic ectoderm, has also the potency of becoming epidermal and sometimes dental epithelium. Divergent differentiation in this plastic ectoderm-like tissue accounts for the continuity of young nerve tissue and epidermis which is often seen in this tumor. In its later stages of differentiation teratomatous neural tissue resembles the spongioblastic mantle zone and the developing ependyma of the embryonic nervous system at different stages.

FROM THE AUTHOR'S SUMMARY.

VIRUS OF INFECTIOUS ECTROMELIA. F. M. BURNET and D. LUSH, J. Path. & Bact. **42**:469, 1936.

The virus of ectromelia inoculated in high concentration intranasally in rats produces foci of infection and multiplies in the olfactory mucosa. In a high proportion of the rats small amounts of virus can be detected in the olfactory bulbs. After infection circulating antibodies appear, and the rats are resistant to reinfection. In a rat in which the olfactory apparatus was completely undeveloped no infection occurred. The possible significance of the olfactory system as a point of attack for viruses is discussed.

FROM THE AUTHORS' SUMMARY.

PRIMARY DIFFUSE ALVEOLAR CARCINOMA OF THE LUNG. S. WEISSMANN, Frankfurt. Ztschr. f. Path. **47**:534, 1935.

Two cases of primary carcinoma of the lung are described. The tumors had involved both lungs. Histologically the growth was found exclusively within the alveoli, the tumor cells having formed the inner lining of the alveoli. There were metastases in the hilar lymph nodes. The literature on similar cases is reviewed, and the conclusion is reached that tumors of this type arise on the basis of a faulty embryonal anlage of the alveolar epithelium. Such an epithelium is potentially malignant and if present in a person who has "a general disposition toward tumor growth" may at any time give rise to carcinoma. (Weissmann believes in the epithelial nature of the cells lining the alveoli.)

OTTO SAPHIR.

GLIOMAS. H. J. SCHERER, Virchows Arch. f. path. Anat. **294**:790, 795 and 823, 1935.

In the first of three articles, which constitute the opening contributions to a promised thorough investigation of gliomas, Scherer criticizes the current cytologic and histologic trends in the study of this group of tumors as being limited too narrowly to consideration of the tumor cells. He insists that the tumor cell does not exist—that there is no specific tumor cell with characteristics that distinguish it from the normal cell. He maintains that a tumor is a dynamic whole or organization or organism, the constituents of which react to and on each other, and that the tumor as a whole reacts to its environment just as the host reacts to the tumor and to his environment. The phenomena of the growth, structure and the reactive processes of the tumor as a whole are more important than the morphologic character of the tumor cells. It is from this standpoint that he proposes to investigate gliomas. For his purpose he has used, not operative material, but necropsy material in which the tumor could be studied in its entirety and in relation to the brain. Sections of the entire neoplasm stained by the Nissl method have been employed. Other neurohistologic methods have been used as indicated.

The second contribution, the title of which may be translated "Limitations of Cytodiagnosis of Brain Tumors," is a more specific critique of current methods based on the study of two neoplasms termed "glioblastoma multiforme ganglioides." The tumors contained mononucleated and multinucleated giant cells of a type usually interpreted as immature and atypical ganglion cells. Tumors of this type have been described in the recent literature under the names "ganglioneuroma," "ganglioglioma," "astroblastoglioma," "retothel sarcoma" and still others. The giant cells have none of the essential characters of ganglion cells and are not ganglion cells. He severely criticizes the designations "spongioblastoma" and "glioblastoma multiforme" as representing a hodgepodge of neoplasms that have in common only such morphologic immaturity and pleomorphism of their cells that the origin of the cells cannot be determined.

In the third and longest contribution, entitled "Angioblastic Gliomas," the author leaves the field of polemics and proceeds to observations of his own. He describes in detail the histologic features of, and discusses the significance of, peculiar vascular structures in gliomas. These have been previously described, but, he thinks, their significance has not been recognized. The structures are of two types. One type consists of a localized group of capillary and precapillary vessels formed by the intimal or adventitial capillarization of a restricted portion of a larger vessel. The other type is glomerulus like. It consists of a convoluted capillary vessel with proliferated endothelium. In many of the structures an afferent and an efferent vessel by means of which they are united to an arteriole can be recognized. These structures have the following situations: about areas of necrosis, where they are polarized toward the necrosis; in non-necrotic tumor tissue; in the advancing margin of the tumor, where they are directed toward the tumor and where they can be differentiated from dilated preexisting vessels.

They may undergo fibrosis and lead to the formation of fibrous nodules. In the tumor tissue they may be covered by tumor cells, which here reveal greater growth activity than in other parts of the tumor. The glomerular vessel and its covering mass of tumor cells form a fairly sharply circumscribed cellular nodule. The structures described occur in groups in localized areas. The evidence equal age of the structures in a group indicates their sudden and eruptive formation as a reaction to local growth stimuli. They were seen most often in two types of gliomas, although in smaller number they have been seen in other types variously named in the current classifications. Of the two predominating types, one is a large infiltration tumor arising in the white matter of the cerebrum. These tumors are histologically and clinically highly malignant; they are cellular and pleomorphic. The other type is smaller, more sharply circumscribed, and arises in the white matter of the cerebrum or brain stem. Tumors of the same cellular character as these two groups may reveal none of the vascular structures. The vascular complexes cannot be and are not used as a criterion in classifying gliomas. There is no characteristic angioblastic glioma. The term is used in a purely descriptive manner to cover structures that may arise in any form of growing glioma and that are the expression of biologic phenomena in restricted areas of the tumor.

O. T. SCHULTZ.

LIPOMAS OF THE BRAIN AND SPINAL CORD. L. KRAINER, Virchows Arch. f. path. Anat. **295**:107, 1935.

Krainer reports two lipomas of the brain and tabulates these with sixty-five others from the literature. He mentions five others, the original reports of which were not available, and two in lower animals, one in a rabbit and one in a duck. In the tabulation the lipomas are grouped according to their location. The tumors are situated in the cisternal enlargements of the subarachnoid space, where they are closely attached to the vessels or nerves traversing the space or are attached to the choroid plexus. They may grow along the nerves or vessels into the brain or cord tissue and thus simulate infiltrative growth. They rarely present evidence of progressive growth. They are maldevelopments derived from remnants of the primitive meninx by a process of heteroplastic differentiation.

O. T. SCHULTZ.

EXPERIMENTAL CARCINOMA OF THE LIVER. T. SASAKI and T. YOSHIDA, Virchows Arch. f. path. Anat. **295**:175, 1935.

Three hundred and sixty white rats were fed daily ortho-amino-azotoluene dissolved in olive oil and mixed with unpolished rice. Without exception multicentric carcinoma having its origin in liver cells developed in the animals that lived long enough. From 255 to 300 days were necessary for its development. With smaller quantities of the chemical longer periods were necessary. If the animals were fed the chemical for four months the carcinoma continued to develop and metastasized to the lungs or lymph nodes after the feeding was interrupted. Animals were killed at various intervals for histologic study; progressive proliferation of liver cells was observed. The hepatoma developed in eighty-four animals. Occasionally it was associated with carcinoma of biliary epithelial origin. In four animals only the latter occurred.

O. T. SCHULTZ.

SEROLOGY OF TUMORS. F. BREINL, V. KINDERMANN and E. CHROBOK, Ztschr. f. Immunitätsforsch. u. exper. Therap. **86**:260, 1935.

The serologic relationships between immune serum against cancerous tissue and alcoholic extracts of cancerous and of normal human organs were studied by means of the complement fixation test. Close affinity was found to exist between cancerous extracts of different organs, and frequently reactions took place between the anticancerous serum and the noncancerous organs of persons with cancer.

The nonspecific lipoid antibodies of cancerous antiserum could be removed by treatment with alcoholic extracts of normal organs or with weak dilutions of a standard solution of formaldehyde, thus making the antiserum more cancer-specific.

I. DAVIDSOHN.

THE TUMOR ANTIGENS. F. BREINL and E. CHROBOK, Ztschr. f. Immunitäts-forsch. u. exper. Therap. **86**:274, 1935.

The difficulty of producing tumor-specific immune serum is attributed to a great extent to the complex antigenic structure of tumor tissue. Breinl and Chrobok succeeded in removing some of the nonspecific substances by treating alcoholic extracts of tumor tissue with charcoal and subsequently washing the charcoal with benzene. While the chemical nature of the tumor-specific substance was not determined, it was established that it is not a phosphatide or any other nitrogenous substance or a carbohydrate. Cholesterol esters were present in the active fractions of the extracts and absent in the inactive.

I. DAVIDSOHN.

Medicolegal Pathology

BLOOD GROUPING IN FORENSIC MEDICINE. A. O. GETTLER and H. E. KRAMER, J. Immunol. **31**:321, 1936.

Gettler and Kramer advise against the use of the blood grouping of partially decomposed and contaminated blood stains because: (*a*) in one of eight blood stains on metal agglutinin B could not be detected after one month, and in another stain agglutinogen B disappeared from blood AB; (*b*) two incorrect groups were obtained in eighteen two day blood stains on cloth (an A reacted as an O and an AB as an A; (*c*) the same number of erroneous results was found in eighteen stains on cloth kept for thirty-seven days (an O behaved like a B and an A like an O); (*d*) in eighteen blood samples that were kept for two months at room temperature and underwent putrefaction, fourteen faulty results were obtained (on two occasions O reacted as A; A reacted on two occasions as B, on four occasions as O and on one occasion as AB; B reacted on two occasions as O, and AB reacted similarly on three occasions).

I. DAVIDSOHN.

GROUP DETERMINATION ON DRIED BLOOD SPOTS AND TRACES OF SALIVA. A. W. RADCLIFFE, J. Lab. & Clin. Med. **22**:191, 1936.

Radcliffe prepared thirty blood stains and thirty saliva stains with blood and saliva taken from thirty different persons. Later he attempted to determine the groups of the stains on cloth, identified only by number. Each blood stain was tested for its agglutinogen and agglutinin content; the saliva stains, naturally, only for their receptor content. The agglutinogens were tested for by determining the absorbing power of the stains on the group O serums, using unstained cloth as a control. As far as the blood stains were concerned, in twenty-four of the thirty cases the correct group could be determined, and in six the results were inconclusive, but in no case was an erroneous diagnosis made. As far as the saliva stains were concerned, in twenty-six of thirty cases the correct group could be determined; in one case the reactions were inconclusive, and in three cases false diagnoses of group O were made, but these could not be considered errors, since the subjects were nonsecretors. Some preliminary tests showed that the method was also suitable for demonstrating the presence or absence of the property M in blood stains.

A. S. WIENER.

ON THE EXCLUSION OF MATERNITY. L. HIRSZFELD, Deutsche Ztschr. f. d. ges. gerichtl. Med. **27**:70, 1936.

Hirszfeld cites two cases in which he was able to prove nonmaternity on the basis of Bernstein's theory of the heredity of the blood groups. In one case

two new-born infants had been interchanged in a hospital, and the mixup was straightened out when it was shown that one of the infants belonged to group AB and its supposed mother to group O. In the second case a woman 54 years of age attempted to deceive her youthful husband, but the fraud was disclosed by the blood tests. A list of combinations which exclude maternity is given for the classic blood groups, the subgroups of A and B and the M-N types. A. S. WIENER.

RESEARCHES ON CARBON MONOXIDE HEMOCHROMOGENS. O. SCHMIDT, Deutsche Ztschr. f. d. ges. gerichtl. Med. **27**:82, 1936.

A short historical discussion of hemochromogens precedes a highly technical chemical and physical analysis of them. The spectrum of carbon monoxide hemochromogens appears after reduction of a pure hematin solution only in the presence of protein. The hemochromogens frequently appear when hemic waste products are treated with nitrogen-containing reagents. The hematins are highly reactive bodies and form addition products because they contain an unsaturated iron radical. When blood from the victims of carbon monoxide poisoning was kept in the icebox three months, it became more alkaline with decomposition, and hemochromogens developed, which were demonstrated spectroscopically.

GEORGE RUKSTINAT.

POSTMORTEM DISCOLORATION OF THE IRIS. G. SCHRADER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **27**:105, 1936.

The color of the eyes in unknown corpses becomes exceedingly important. Immersion in water may alter the color so that identification is difficult. Such a color change was noted in five corpses subjected to the action of water for from twenty-four hours to eight weeks. The true color of the eyes of these corpses had been noted as blue or gray-blue by relatives, but varying shades of brown were recorded by the medical examiners. This discoloration was most intense peripherally and occurred even before the cornea had become cloudy. The alterations were ascribed to postmortem imbibition of blood pigment, with hypostasis in the head playing a rôle, since in a floater the abdomen is highest in the water. The contributing factors are maceration by water, diffusion of choroidal pigment, effect of the temperatures of air and water and increase in the turgor of the ocular bulb so that it may not sink inward for weeks. Experiments on the eyes of animals are carried out with difficulty since most of them have brown eyes. A series of tests was run on swine's eyes, however, but results were obtained only when water at a temperature of 25 degrees C. was used.

GEORGE RUKSTINAT.

Technical

CAPSULES ABOUT HEMOLYTIC STREPTOCOCCI AS VISUALIZED WITH INDIA INK OR AZO-BLUE. E. M. BUTT, C. W. BONYNGE and R. L. JOYCE, J. Infect. Dis. **58**: 5, 1936.

The size of the capsular zone about the hemolytic streptococcus in india ink is partly dependent on the character of the fluid used in diluting the ink. The largest zone is seen in india ink diluted with 6 per cent dextrose, while in water-diluted ink the capsular zone is small or not present. Azo blue may be substituted for india ink in the demonstration of bacterial capsules.

FROM THE AUTHORS' SUMMARY.

THE INFLUENCE OF TEMPERATURE ON ISO-AGGLUTINATION. I. M. TOWNSEND and A. F. COCA, J. Lab. & Clin. Med. **21**:729, 1936.

About 10 per cent of undiluted serums belonging to blood groups A and B cause only slight clumping of the corresponding agglutinable cells, or apparently

none at all, at body temperature (40 C. [104 F.]). Transfusion of incompatible blood into such patients might be expected to be followed by only mild symptoms. The quantitative test used in the detection of the dangerous universal donor may be properly carried out at body temperature, the incidence of the dangerous universal donor being estimated by this method at approximately 3 per cent of persons with serum of group O. FROM THE AUTHORS' SUMMARY.

TECHNIC FOR REMOVAL OF THE ORGANS OF THE NECK. W. S. STANBURY, J. Tech. Methods, 1936, no. 15, p. 42.

The technic involves the careful dissection and ligation of the larger carotid branches cut in the process of removal of the organs, taking particular pains to avoid injury to the external maxillary arteries. The approach is through a primary V-shaped incision extending from the acromial ends of the clavicles to a point just below the junction of the manubrium with the body of the sternum. After removal of the thoracic viscera, the skin is reflected from the larynx and anterior muscles of the neck as far up as the ramus of the jaw. The trachea and upper portion of the esophagus are elevated and dissected away from the cervical spine. The inferior thyroid, superior thyroid and lingual arteries are ligated in turn and severed distally. The posterior pharyngeal wall is divided horizontally at about the level of the third cervical vertebra. The larynx and trachea are returned to the neck, and a long, slender, pointed amputation knife is passed upward under the skin to a point just behind the symphysis of the lower jaw, where it is carried through the floor of the mouth until the point appears beneath the tip of the tongue. The mylohyoid, geniohyoid, digastric and genioglossus muscles are divided by carrying the knife with a sawing motion down first one ramus of the jaw and then the other to a point just anterior to the masseter muscle. The tongue is grasped and drawn down. The remaining muscular attachments are severed under direct vision. In restoring the body, the mouth and pharynx are packed tightly with absorbent cotton, and the neck is padded to natural proportions. This technic will not interfere with the subsequent embalming of the face.

MEDIUMS FOR BACILLUS TYPHOSUS. E. R. JONES, J. Path. & Bact. **42**:455, 1936.

Bacillus typhosus and organisms of the typhoid group grow freely on brilliant green-eosin-lactose agar at concentrations of the dyestuffs which completely inhibit the growth of small inoculums of Bacillus coli. Sodium tetra-thionate broth is a suitable fluid enrichment medium for organisms of the typhoid group. Strains of the dysentery bacteria tested were completely inhibited by this medium. The combined use of tetra-thionate broth and brilliant green-eosin-lactose agar has proved much superior to the use of MacConkey's medium for the isolation of organisms of the typhoid-paratyphoid group from the urine and feces of patients suffering from enteric fever. FROM THE AUTHOR'S SUMMARY.

DEMONSTRATION OF GOLD IN ANIMAL TISSUES BY THE METHOD OF PHYSICAL DEVELOPMENT (GERM METHOD OF LIESEGANG). W. J. ROBERTS, Bull. d'histol. appliq. à la physiol. **12**: 344, 1935.

A method is described for the detection of gold and salts of gold in animal tissues by the establishment of a layer of silver around a center of gold. Frozen sections of tissues fixed in a standard solution of formaldehyde diluted 1:5 are immersed in a 2 per cent solution of silver nitrate in 10 per cent acacia and reduced in a similar solution of 1 per cent hydroquinone. The sections are then fixed in 5 per cent sodium hyposulfite, dehydrated and mounted, with or without counterstaining. This results in a visible precipitate of silver on otherwise invisible gold particles. The technic is rapid, reliable and much more sensitive than spectrographic methods. Illustrations are given showing gold in the cells of the renal tubules and the reticulo-endothelial system after parenteral injection.

NORMAND L. HOERR.

Society Transactions

NEW YORK PATHOLOGICAL SOCIETY

N. Chandler Foot, *President*

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Milton Helpern, *Secretary*

Uterine Papillary Cystadenoma with Origin in Rests of the Wolffian Body: Report of a Case. C. C. Weitzman (by invitation), S. H. Polayes and F. Sheer (by invitation).

A survey of the literature reveals the rarity of cases of papillary cystadenoma of the uterus.

Four theories are to be considered in discussing the origin of this type of tumor relating, respectively, to: (1) the wolffian system (von Recklinghausen, Mercade, Dvorzak), (2) the müllerian duct (Cullen, Harnbleu), (3) the peritoneum (R. Meyer and Blount) and (4) the hyperplasia associated with chronic inflammation (Chiari, Schauter).

In view of the fact that R. Meyer has noted that the incidence of wolffian body rests in adult uteri is 22 per cent, it is remarkable that one so rarely finds in the literature reports of tumors arising from these rests. We have observed a tumor of this type.

A 38 year old Peurto Rican woman, married for fourteen years, was admitted to the Cumberland Hospital, Brooklyn, service of Dr. H. T. Wikle. Her chief complaint was that she had a painless mass in the lower part of the abdomen. The menstrual period was normal. She had had one pregnancy, which ended in a spontaneous miscarriage. There was a suprapubic mass about 9 by 12 cm. in diameter, which was a part of the uterus. The adnexae were not palpable. The Wassermann reaction of the blood was negative. The Aschheim-Zondek test was negative. At operation a "fibromyoma" and bilateral tubo-ovarian disease were found, for which a supracervical hysterectomy and bilateral salpingo-oophorectomy were performed.

The pathologist's report was as follows: An intramural pale-pink mass measuring 5 by 6 by 4 cm. occupied the greater portion of the uterine body and fundus. It was trabeculated and contained a large number of discrete cystic structures of varying size, which were filled with a clear colorless mucoid fluid. The main wall was completely surrounded by myometrium and merged imperceptibly with it.

Microscopically, the tumor was composed of interlacing cystic and papillary structures, which were lined by epithelium and supported by a stroma of muscle and connective tissue. The lining cells varied from low cuboid to tall columnar, and some were ciliated and some were not. Nowhere in the sections was endometrial stroma demonstrable. There were ductlike and glandlike structures of similar histologic description adjacent to the interstitial portion of the right tube, which morphologically resembled epoophoron (wolffian body rests). Some of these were papillated and showed striking resemblance to the uterine tumor.

The tubes and ovaries were the seat of a chronic inflammatory process.

In our opinion, the tumor probably had its origin in rests of the wolffian body, as evidenced by (1) the failure to trace continuity to either the tubal mucosa or the endometrium, (2) the absence of endometrial stroma, (3) the histologic similarity of the tumor to epoophoron and (4) the location of the tumor.

Sudden Death in a Case of Schistosomiasis of the Lungs. B. M. Vance.

The following case from the Chief Medical Examiner's Office, New York City, is an example of sudden death from pulmonary schistosomiasis.

A Puerto Rican woman 28 years of age suddenly became ill and died before she could be removed to the hospital. Her previous medical history could not be learned. She had been in New York City for seventeen months, but whether or not she had visited Puerto Rico in this period was not ascertained.

The necropsy disclosed a woman 4 feet, 11 inches (150 cm.) in height, weighing about 130 pounds (59 Kg.) and showing a distinct tendency to obesity. No lesions of the skin were present. The liver was large and fatty and weighed 2,100 Gm. The lungs together weighed 850 Gm. and were cyanotic, congested and edematous, with considerable foamy fluid in the bronchi. The diagnosis of acute fulminating pneumonia was made at necropsy, and schistosomiasis was not suspected.

Histologic examination of the lung tissue disclosed scattered small nodules composed of epithelioid cells and foreign body giant cells, surrounded by leukocytes, lymphocytes and eosinophils. Eggs of Schistosomum Mansoni with long lateral spines were found here and there in these nodules. The rest of the lung was the seat of acute pneumonitis, with polymorphonuclear leukocytes and eosinophils in the alveolar walls, while the alveoli were filled with numerous red blood cells or edematous fluid containing large spherical cells. A few nodules containing ova were found in the periportal spaces of the liver. The cerebral subarachnoid space was infiltrated with a few large spherical cells, probably as the result of toxemia.

The development of the lesions in the lungs is difficult to explain because it was not possible to obtain any information concerning the medical history of the deceased. It is believed that death was due to the toxemia resulting from the infection of the lung by S. Mansoni.

DISCUSSION

ALFRED PLAUT: I should like to know how frequently at the medical examiner's office or at hospitals where autopsies are made on many persons from the West Indies schistosomiasis is found. I remember having seen similar lesions in appendixes when an infection with schistosoma had not been suspected. In one instance the uterine cervix, also, contained calcified eggs. I should like to ask further how the spines in Dr. Vance's preparations looked in the paraffin sections, whether the spines always appeared in the position typical for S. Mansoni. I once thought I could see lateral as well as polar spines in the same side. The late Professor Fülleborn, however, convinced me that when one dissolves the tissue with antiformin and thus can examine the free ova, every one of these shows the spine in the position characteristic for S. Mansoni. From paraffin sections one can draw no conclusions as to the position of the spine.

EUGENE CLARK: My associates and I had the opportunity two years ago of studying a Puerto Rican 21 years of age, who left Puerto Rico at the age of 9. She was admitted to Bellevue Hospital in congestive heart failure and died a few hours after admission. The case was presented before this society by me two years ago (*Proc. New York Path. Soc.*, 1934-1935, p. 18). At necropsy she exhibited lesions of schistosomiasis Mansoni throughout the abdominal viscera, and, more noteworthy, an obiliterating schistosomal arteritis of the small pulmonary vessels. As a result of this, hypertrophy of the right ventricle of the heart occurred and led to congestive heart failure.

I have some slides of sections of the lungs which I should like to show. In the lungs, schistosomal granulomas were limited to intravascular and perivascular positions. The section shown (lantern slide) is from a lesion of this type, and its vascular nature is recognized by the presence of remnants of the arterial wall. The section is stained by the Weigert technic, and a portion of the internal elastic membrane is visible. The lumen of the vessel is obliterated by granulomatous tissue containing a schistosomal ovum, and as a result of partial destruction of its wall the vessel has undergone aneurysmal dilatation.

Study of serial sections reveals that these lesions occurred in vessels approximately 200 microns in diameter and that intimal thickening of a severe degree and of a nonspecific nature occurred in the vessels, proximal to the portions obliterated by the schistosomal granulomas. In the larger vessels advanced atherosclerosis was present.

ANDREA SACCONE: I agree with Dr. Plaut as to the difficulty of making the diagnosis on ova of the type shown in the photograph. Probably the slide shown by Dr. Vance gives under the microscope the real appearance of S. Mansoni, but I am not convinced as to the diagnosis from the appearance on the screen. There is no question of a parasitic infestation, but for years it has been known that infestation with Paragonimus Westermanii is common in the lungs of people who live in tropical places. Otani and Yamagiwa made an accurate clinical study of the disease, and Naunyn reported a case in a man in Strasbourg, France, who had lived in California for fifteen years. So I think more accurate investigation is needed before this is accepted as an infestation of the lung by S. Mansoni rather than an infestation by some other type of trematode.

SHELDON A. JACOBSON: The Hospital for Joint Diseases gets a large proportion of its patients from the Harlem district, in which there are many patients of West Indian origin. In four and a half years in the laboratory of that hospital only one case of what is called schistosomiasis came to attention at autopsy. It was histologically very similar to that reported by Dr. Vance. The lung was the seat of the chief infestation, and the colon and liver were also invaded, but the disease was not the cause of death. Death was due to some unrelated condition. At the time, the condition was diagnosed as schistosomiasis, but I cannot definitely state that it was not an infestation with P. Westermanii, as the last speaker said.

B. M. VANCE: In answer to the question of Dr. Plaut, I may say that the diagnosis of schistosomiasis was not made until after the lung was sectioned and all the tissues were fixed in solution of formaldehyde U.S.P. In this case the embedding material was pyroxylin (celloidin) and not paraffin. No attempt was made to separate the ova from the lung by digestion. In my opinion, however, the ova in the sections possess lateral spines and resemble the ova of S. Mansoni closely enough to justify the diagnosis.

Dr. Saccone has referred to infestation of the lungs by P. Westermanii, a trematode of a group different from that of Schistosomum. The former does not possess ova with spines and hence could not be the infecting agent in this case.

BOTRYOMYCOSIS IN MAN. ALFRED PLAUT.

Botryomycosis as a disease of man seems to be exceedingly rare and has received little attention. Current textbooks of bacteriology seldom contain the term in the index. The disease is frequent in horses, notably after castration, and has been known for decades but has been definitely described in man in only a few cases.

Since, according to old and recent studies, Botryomyces is only a special form of Staphylococcus, one might ask why it should be important to pay attention to this extremely rare form of staphylococcic disease in man. In order to show the practical importance, the following case is briefly reported.

A middle-aged diabetic woman felt pain in the left lower quadrant of the abdomen, with a dragging sensation, and a palpable mass developed. At operation the mass was found to be situated entirely in the abdominal wall, and on incision it proved to be an abscess with omental adhesions under it. On examining sections from the abscess under low magnification, one had the impression of seeing characteristic actinomycotic granules. Closer examination, however, demonstrated the absence of fungous formations and the presence of many gram-positive coccus-like bodies in the centers of the granules. The periphery of each granule was formed by a homogeneous mass, obviously consisting of coalescing dead cocci. Therefore the diagnosis of botryomycosis was made.

The importance of this case and of the recognition of human botryomycosis in general lies in the prognosis. Actinomycosis is a serious disease, fatal when located in inner organs and of long duration even when restricted to nonvital portions of the body. Botryomycosis, however, at least in animals, has a much better prognosis. Lesions in inner organs are rare. The presence of a botryomycotic granule in an artery in this case indicated the possibility of general

spreading. The number of cases of true human botryomycosis is too small to venture any opinion on the prognosis. Including this one, I count only six cases. As far as I can see, in all cases foreign bodies, mostly represented by fragments of bone, have played a rôle. In this case a foreign body was found in the center of the abscess. It looked like a very thin piece of wood. On examination by Dr. Ralph H. Cheney of the biology department of Long Island University, it proved to be a part of the broom-corn plant that is used for the manufacture of brooms and brushes. Obviously, a fragment of a bristle had been accidentally stuck into the skin of the patient, who was a housewife. The character of the foreign body in a botryomycotic lesion might prove or disprove causal connection of the lesion with an accident.

Summary.—A case of true human botryomycosis is reported. On superficial microscopic examination botryomycosis might be mistaken for actinomycosis, and thus an important error might be made in therapeutics and prognosis. Foreign bodies seem to play a rôle in the development of botryomycosis in man.

NOTE.—For a more detailed description of botryomycosis and for the literature see Berger and others (ARCH. PATH. **21**:273, 1936).

DISCUSSION

N. CHANDLER FOOT: Dr. Plaut has brought out an important point in regard to prognosis, and I am sure he is right when he says that cases of this type are being overlooked. I know that in the hospital with which I am associated several cases have been reported as instances of actinomycosis one or two of which I should like to investigate.

PAUL KLEMPERER: Were these granules staphylococci or other bacteria? Is botryomycosis in horses staphylococcic infection? Has botryomycosis in horses a definite histologic picture? I thought that it was the angiomatous character of the granulomatous lesion which was characteristic for botryomycosis, and that the term is used loosely for the telangiectatic granuloma in man.

N. CHANDLER FOOT: Were cultures made from the blood or the abscess?

ALFRED PLAUT: There were no positive blood cultures in this case.

As to Dr. Klemperer's question, the telangiectatic granuloma has nothing to do with botryomycosis. I purposely avoided mentioning it. How granuloma telangiectaticum came to be called botryomycosis is a mystery to me.

The second question is a much more difficult one. I hoped nobody would bring it up. There is a great difference of opinion as to whether these granules are staphylococci. The whole course of the disease is not in favor of their being staphylococcic in origin. Most experimenters have not been able to produce botryomycotic lesions in the animal by means of ordinary staphylococci, but with staphylococci from a botryomycotic lesion—staphyococci one cannot differentiate in culture from ordinary staphylococci—one may succeed in producing botryomycosis. Magron in 1914 wrote a doctor's thesis in Paris on botryomycosis, and he stated that with cultures of Staphylococcus aureus from indifferent sources he was able to produce botryomycosis in rabbits. He used very small doses and introduced foreign bodies. Other authors have not been able to repeat his observations. The question is still unsettled. One point, in my opinion, must not be neglected: The rabbit is not susceptible to infection with cocci grown from botryomycotic lesions whereas, in general, it is the best animal for staphylococcic infection; therefore I feel that there is some difference between the coccus-like organisms which grow in those clusters and produce botryomycosis, on one side, and the ordinary staphylococci, on the other side.

MESONEPHROMA OVARII. WALTER SCHILLER (by invitation).

In the course of the examination of a large number of cystic ovarian tumors certain ones have been noted which, through the character of their lining cells, differed distinctly from ordinary cystomas. Whereas in the latter, both in the serous and in the pseudomucinous types, one finds cylindric epithelium in which each cell is closely applied to its neighbor in a flasklike fashion and all

the component cells form a common linear free margin toward the lumen, the peculiar cystic ovarian tumor under consideration exhibits endothelioid cells as a lining. For the greater part, these are not in mutual contact throughout their lateral borders but have a domelike form, each of them projecting into the lumen in the form of a half circle. With this unusual type of cell as a standard, I collected a series of such tumors until, in the course of a few years, I had found ten. During my trip through the United States, I have added to these two more: one in Philadelphia and one in Chicago.

Many of these tumors are papillary, showing a remarkable structure that in no way resembles that of ordinary papillary cystomas. In the latter one finds relatively large pedicles with multiple relatively small, verrucous papillae, each of which is rounded and contains a rich stroma and many blood vessels. In the new type, on the other hand, are relatively small pedicles, each usually supporting one large delicately formed papilla, which contains scarcely any connective tissue stroma and only one capillary loop. This structure, which recurs regularly in almost every case and which may be demonstrated in almost all instances (although there may be certain morphologic variants), reminds one of an immature embryonal renal glomerulus.

If one sides with Kaufmann, R. Meyer, Kermauner and others who deny the possibility and the existence of an endothelioma of the ovary, it is easy to derive these characteristic structural elements of the new type of tumor from embryonal glomeruli. Furthermore, the endothelioid lining of the cysts of this new type shows no intimate connection with blood or lymph channels and no evidence of having originated from such channels.

In speculating as to the origin, the pronephros cannot come under consideration, for it has disappeared by the time the gonads have begun to develop. The metanephros has no topographic relationship to the growth. Therefore there remains only the mesonephros, in the immediate vicinity of which the gonads are developed. The separation of the two organs, the broad surfaces of which originally abut on each other, is brought about by the infolding of the two plicae by means of which the ovary is at first separated from the mesonephros and later attached to it by the remaining pedicle. This fact does not exclude the possibility that these plicae might cut too deeply into the mesonephros, thus including a bit of the tissue of the latter in that of the ovarian primordium.

A tumor might develop later from this misplaced tissue; the tumor originally shows a glomerular structure, but might later become papillary by overgrowth. The lack of tubules might be explained by the fact that the mesonephric duct, which acts as an "organizer" of the mesonephric tubules, is lacking in the tumor. In the cases in which the growth is malignant, a parenchyma is formed consisting of a network of delicate fusiform cells with a minimal amount of connective tissue stroma. This is in sharp contrast with the carcinomatous degeneration noted in the malignant cystoma, which forms plump, purely epithelial, homogeneous masses of carcinoma cells, which are sharply set off from the relatively broad septums of connective tissue in which they are embedded.

Macroscopically, the mesonephroma is of a relatively light color and soft in consistence (pseudosolid) with many extensive and largely liquefied foci of necrosis. The incidence is distributed throughout all age groups; the youngest patient in the series was an 8 month old girl and the oldest a 69 year old woman. In three cases observed to date the growth has proved to be nonmalignant; in seven it was highly malignant, with peritoneal extension. In one case the tumor was connected with a dermoid; in another the tumor formed an integral portion of a malignant embryoma. In one case the mesonephroma developed entirely intraligamentously, as would the usual parovarian cyst, without involving the ovary itself. This finding is also appropriate for strengthening the hypothesis as to the origin of the tumor from the mesonephros.

DISCUSSION

PAUL KLEMPERER: I think this tumor is perfectly clear from the illustrations of Dr. Schiller; one is only surprised that it has not been described previously, perhaps not under the same name, and I should like to know whether Dr. Schiller

has found any tumors resembling this type recorded in the literature, and, if so, under what term. When I try to recall my own experience, I do not remember anything of this kind, but the question is asked in order to help me know what possible error I may have made, and what tumors I should review in order to find this type, which I probably have called by an entirely different name and misdiagnosed. Is there any tumor of the testis which shows the same type of arrangement? It is plausible that the same tumor could arise in the testis. I feel the members owe Dr. Schiller gratitude for calling their attention to this type of tumor, and I think it is remarkable that one can still discover a new tumor of the ovary.

ALFRED PLAUT: May I ask whether Kermauner has described in any way tumors of this type in the volume on ovarian tumors? I cannot remember seeing any tumor of this character, and I wonder whether I should get out my slides on cystoma in order to find an overlooked case. I should not be astonished if in the near future some one in this society finds such a tumor; you may recall what happened after Robert Meyer's publication of a description of the Brenner tumor of the ovary, and how reports of cases came in one after the other at that time.

FRANK SPIELMAN: Are these tumors accompanied by any change in the secondary sex characteristics of the patient, perhaps suggesting some internal secretory action?

N. CHANDLER FOOT: In conversation with me the other day Dr. Schiller told me that Kermauner used to say about new findings, "I probably have seen it in my material, but I did not observe it." I think that is a pertinent commentary on this work.

WALTER SCHILLER: In regard to the first question, I have seen in the literature photomicrographs of tumors classified as multilocular papillary cystoma, and the tumors showed projections and cysts of this type and the very characteristic endothelial-like lining epithelium. I am convinced that these tumors were of this type.

The two cases I have seen in this country have been characteristic. The first one was shown to me by a gynecologist in Philadelphia, who said, "It looks like a papilloma, and it looks like a cystoma, but it does not fit either," and I said, "That is a mesonephroma." The second case I found in Chicago. The gynecologist said, "We have a tumor here which we thought might be an arrhenoblastoma, but it does not look typical. Although I know that there are many various types classified under that name, this tumor does not fit in very well." It was a typical mesonephroma.

Concerning the question of testicular tumors, I have not myself seen many testicular tumors, for my material is mostly from women. I tried to get hold of as many testicular tumors as possible, and I found in teratoid tumors of the testicle small parts which look like mesonephroma, but they were too small to be convincing, and I think that one will have to do accurate research in the future to prove whether or not the mesonephroma occurs in the testis.

I never have found any evidence of hyperproduction of normal hormones or of production of pathologic hormones in tumors of this character. Clinically, the malignant tumors were diagnosed as carcinoma of the ovary; the benign ones, as cystoma of the ovary. Some malignant ones were considered only as malignant growths of the small pelvis. An interesting case was the first one I mentioned, that of a little girl of 8 months brought into the dispensary by her mother with the diagnosis of precocious menstruation. The hymen was investigated, and a mass of tissue was found behind it. An exploratory excision was made. The first photomicrograph was from the tumor of this 8 month old girl. She died a few months later from multiple metastases. I never was able to observe hormonic changes in any of the cases in my series.

I think, if all would review the group of multilocular papillary cystomas and the group of malignant tumors of unknown origin, probably many would be able to find more tumors of this kind.

CHICAGO PATHOLOGICAL SOCIETY

CARL W. APFELBACH, *President*

Regular Monthly Meeting, Jan. 11, 1937

EDWIN F. HIRSCH, *Secretary*

EXPERIMENTAL PRODUCTION OF BRONCHIECTASIS IN DOGS. W. E. ADAMS and L. ESCUDERO.

Bronchiectasis, although described by Laennec as early as 1819, is difficult to produce experimentally. In 1930 D. T. Smith, and more recently J. Weinberg, reported experiments whereby bronchiectasis of the lungs was produced in rabbits. The dogs used in our experiments were divided into two groups. In the first group, consisting of four dogs, several divisions of a primary bronchus were injured by being cauterized with a thermal cautery or with a 10 or 35 per cent solution of silver nitrate. At the same bronchoscopic operation, 1 cc. of a brain broth culture containing aerobic and anaerobic organisms grown from the sputum of a patient with a chronic abscess of the lung was injected into the injured lobe. Most of these animals were infected from three to five times at from five to seven day intervals and were killed at from three and a half to six weeks after the first infection. In the second group, consisting of seven dogs, the procedure was varied in that complete atelectasis of the opposite lung was produced previous to the injury and infection. The atelectasis was accomplished by completely occluding the primary bronchus of that side, using the silver nitrate technic. The animals died or were killed at from three to six weeks after the first infection. The infection usually was repeated three or four times. The lesions produced in both groups were similar. Partial stenosis of the injured air passages developed, and distal to this, saccular and cylindric dilatations of the bronchioles to varying extents and peribronchiolar infiltration. No changes were noted in the uninjured bronchioles. The lesions in the dogs of the second group were larger than those in the first. The intrapleural negative pressure in the second group was increased by from 75 to 100 per cent (more negative). Smith used various organisms and found the spirochete the only one suitable for producing bronchiectatic lesions. Weinberg produced the disease by obstructing a bronchus with a sterilized sand burr, introduced through a tracheotomy wound.

Complete or incomplete occlusion of a primary bronchus by the silver nitrate technic does not lead to development of bronchiectasis or abscess unless pathogenic organisms are present. The factors involved in these experiments are: infection, aerobic and anaerobic; partial stenosis of a secondary bronchus, and increased intrapleural negative pressure obtained by complete stenosis of the opposite primary bronchus, accompanied by total atelectasis. In the first group, the first two factors were present, while in the second all three were present.

In clinical bronchiectasis, atelectasis occurs regularly. Thus, bronchial occlusion produced by an intrinsic or an extrinsic factor has been present. Increased intrapleural negative pressure is therefore present in clinical bronchiectasis. The experiments reported here reveal, however, that this factor is unnecessary in the production of the disease, although the lesions produced are more severe when the intrapleural pressure is more negative.

DISCUSSION

PAUL CANNON: Has the lining epithelium of the bronchiectatic lesions in dogs undergone metaplasia?

S. ROSENTHAL: Were abscesses formed in the lungs by injections of the cultures?

W. E. ADAMS: The lining epithelium of these lesions was flattened, but it never became squamous. The simple introduction of culture material without pressure did not produce abscesses.

A Rare Malformation of the Liver. G. L. Fite.

A curious histogenic malformation of the liver was presented, in which there was great distortion of the lobulation, with the columns of liver cells frequently taking a tubular arrangement. In addition to large hematopoietic foci and much iron pigment, there were some striking large multinuclear cells, which appeared to be syncytial groups of liver cells with an acinar arrangement of the nuclei.

DISCUSSION

R. H. Jaffé: The conditions seem to me to be those of fetal hepatitis.

Actinomycotic Abscess of the Brain. Howard Zeitlin and B. W. Lichtenstein.

The report was published in full in the January 1937 issue of the Archives, page 58.

Calcium Metabolism in Scleroderma. Theodore Cornbleet.

In recent publications on scleroderma there has been discussion of the relationship of this condition to hyperparathyroidism. The focal point of the discussion has been Leriche's practice of parathyroidectomy for scleroderma. There are differences of opinion as to the degree of improvement following resection of the parathyroid glands. The results indicate some improvement, but later there is no further improvement or there is a relapse.

Leriche's contention that hyperparathyroidism is a factor in scleroderma is based more on inductive reasoning than on consideration of the usually accepted criteria. Three characteristics are generally found in hyperparathyroidism: a high calcium and a low phosphorus content of the blood, hypercalciuria and a negative metabolic calcium balance. Some have found that the blood calcium may be high or low, but generally normal, and that the blood phosphorus is usually slightly above normal. The urinary calcium is far below that considered as normal. The data on the calcium balance are meager. For this reason, a study of this aspect of scleroderma was undertaken.

The results revealed marked retention of calcium, i. e., a positive balance. In keeping with other reports, the urine contained little calcium. Large doses of vitamin D were given, and the urinary calcium thereupon greatly increased. The fecal calcium remained stationary. The augmented urinary calcium sufficed to reverse the positive into a negative calcium balance. Observations on each patient showed that after sufficient vitamin D had been given the effect continued for a long time, even after treatment was discontinued.

The condition of the patients was improved after vitamin D had been administered for two or three months. Nine patients were observed, some for as long as fourteen months. All showed improvement after the first three months. The skin and muscles became softer and more pliable. The hands could be used again for their accustomed work. The improvement, however, was limited. Not even in the longest-treated patient was there a cure. Perhaps, after a longer time, as more and more calcium is removed from the pathologic deposits of the substance, the tissues will approach closer to their normal state.

Histologically, the changes characteristic of scleroderma are hyperplasia of the collagen and deposition of calcium salts. The deposition of calcium seems to be secondary to the changes in the collagen. For this reason, removal of the calcium leaves a residue of hyperplastic collagen. Hence, efforts directed against the calcification leave the patient short of cure.

The report was published in full in the *Archives of Dermatology and Syphilology* (**35**:188, 1937).

DISCUSSION

R. H. Jaffé: Does the skin in scleroderma contain calcium in excessive amounts?

J. P. Simonds: Are there manifestations of renal damage, such as the appearance of albumin or casts in the urine, with large doses of vitamin D?

Theodore Cornbleet: The calcium content of the skin in scleroderma is increased. There were no manifestations of renal damage.

PATHOLOGICAL SOCIETY OF EASTERN NEW YORK

V. W. Bergstrom, *Presiding*

Regular Meeting, Feb. 14, 1936

Arthur W. Wright, *Secretary*

Lipoid Pneumonia: Report of a Case. G. H. Klinck Jr.

An undernourished white girl 6 months of age exhibited signs suggestive of meningitis and appeared dyspneic and cyanotic. Dulness was noted over both lungs posteriorly. The temperature was 102.2 F., and the respirations were 60 per minute.

The child was underweight at birth and had always presented a feeding problem. At 6 months of age she weighed 5,100 Gm. During the fourth month of life she was given one-half teaspoonful of mineral oil as a laxative. From the third month on she received one-half teaspoonful of cod liver oil three times a day. No other medications with oil were used.

After her admission to the hospital signs suggestive of meningitis soon disappeared, but bilateral bronchopneumonia developed. The disease was protracted. The temperature rose at times to 105 F.; on other occasions it returned to normal. A roentgenogram taken three weeks after admission showed the pleura thickened on the right and small foci of bronchopneumonia on the left. Other roentgenograms revealed no further changes until four and one-half months later; then, in addition to the initial findings, localized pneumothorax was noted on the right. Throughout the illness the leukocytes numbered between 20,000 and 30,000 per cubic millimeter. Three days before the patient died, bilateral otitis media developed, and both ears were drained. The temperature rose steadily. Weakness became more marked, and death occurred five months after admission.

Autopsy revealed a poorly developed and poorly nourished white girl 11 months of age, weighing 5,760 Gm. Each pleural cavity contained a small amount of clear fluid. The right lung weighed 210 Gm., and the left 170 Gm. The anterior portions of the upper and lower lobes of both lungs were pink, soft and crepitant. A sharp line of demarcation divided the anterior soft portions of lung tissue from the firm yellow posterior portions. Sections from the posterior portions showed solid, heavy yellowish tissue, from which droplets of oil could be expressed. The bronchioles were filled with yellowish green pus. The remaining organs were not remarkable.

Microscopically, the alveoli, bronchioles and stroma contained many large vacuolated phagocytic cells. Very few polymorphonuclear leukocytes were observed. The condition was essentially a foreign body reaction to oil which resulted in consolidation of the posterior portions of both lungs. By tinctorial and simple chemical methods the vacuoles and the phagocytes were found to contain inorganic oil, which was presumed to be mineral oil. A rough quantitative determination indicated that each gram of the solidified lung substance contained approximately 127 mg. of the oil.

For a complete report of this case see the *Albany Medical Annals* (**55**:71-77, 1936).

Mediastinal Teratoma with Secondary Squamous Cell Carcinoma. R. J. Lebowich.

From the mediastinum of a 22 year old white woman a huge tumor mass was removed surgically. It was encapsulated, lobulated and roughly ovoid, measuring 10.5 cm. in its greatest diameter. At the periphery were many small cysts, which contained thick, glairy mucus. The bulk of the mass was composed of coarsely granular pinkish-gray neoplastic tissue.

Histologically, derivatives of all three germinal layers were observed. The tumor was lined with squamous epithelial cells, which in places were necrotic. Frequent cysts, lined with high columnar epithelial cells filled with mucus, typical salivary gland tissue, several islands of hyaline cartilage, masses of mucoid con-

nective tissue and other structures were also seen. The coarsely granular neoplastic tissue was definitely malignant and proved to be squamous cell carcinoma. The tumor cells were highly neoplastic and were growing rapidly. In only a few places was keratinization evident.

Teratoid tumors of this character usually occur in young adults and grow very slowly. Occasionally, as in this case, malignant changes occur. The origin of these neoplasms is in doubt, but many investigators consider that mediastinal teratomas of this type are probably derived from the third branchial arch.

MULTIPLE MYELOMA: REPORT OF A CASE. S. H. CURTIS.

A married housewife aged 40 first complained of pain in her back and chest and difficulty in walking. For the next four months her condition grew worse until she finally became confined to bed. Several months later she entered the hospital for observation. The family history and the patient's history were not significant. There had been two normal pregnancies. Pain and tenderness on pressure along the spine were the only outstanding symptoms.

Roentgenograms of the skeleton showed many punched-out, smoothly outlined areas of rarefaction in the skull, lumbar vertebrae, ilia, ribs and femurs.

The red blood cells numbered 4,160,000 and the white blood cells 4,800. A differential leukocyte count gave the following percentages: neutrophils, 60; lymphocytes, 35; immature myeloid cells, 5. The blood sugar was 120 mg., the nonprotein nitrogen 37.5 mg. and the blood calcium 12 mg. per hundred cubic centimeters.

The urine had a specific gravity of 1.034. Bence-Jones protein was present. There were traces of diacetic acid and acetone. A few leukocytes and a small number of hyaline casts were present in the sediment.

A diagnosis of multiple myeloma was made, and the patient was given intensive radiation therapy. During the following three or four months definite clinical improvement resulted, but about six months later all the symptoms recurred, and after a brief illness the patient died.

RECURRENT SARCOMA OF THE UTERUS. V. W. BERGSTROM.

A married woman aged 60 was admitted to the hospital because of a tumor of the uterus. Nine years previously she had had cystitis, from which she recovered satisfactorily. Operation revealed in the anterior uterine wall a lobulated tumor growing out into the broad ligaments. Panhysterectomy was done. Histologically, the tumor proved to be a very cellular myoma, not definitely malignant.

The patient made a satisfactory recovery, but nine months later she reappeared with pain in the bladder, frequency of urination, a bearing-down sensation in the pelvis and pain in the back. At operation two small intraligamentous tumors were found, one on each side. Grossly and microscopically, these were rapidly growing malignant sarcomas. A series of treatments with high voltage roentgen rays was given. Five months later the patient again presented herself, complaining of marked exacerbation of all symptoms, particularly of those referable to the pelvis. A large tumor was found, involving the bladder and right ureter. This tumor was removed. It appeared well encapsulated and weighed 1,000 Gm. On section it exhibited soft glistening cut surfaces of a yellowish color and contained a number of large cavities filled with bloody fluid. Histologically, it was a rapidly growing leiomyosarcoma.

MONOCYTIC LEUKEMIA: REPORT OF A CASE. A. W. WRIGHT.

A Jew 50 years of age consulted a physician because of an ulcer on the gingival margin of the right lower jaw. He did not feel sick but had lost about 15 pounds (7 Kg.) in the preceding three or fourth months.

He was stocky, pale, and appeared somewhat undernourished. A large grayish necrotic ulcer from 2 to 3 cm. in diameter was present on the inner gingival margin near the molar teeth. The superficial lymph nodes of the neck, axillae and inguinal regions were moderately enlarged and discrete. The spleen extended from 3 to 4 cm. below the costal margin.

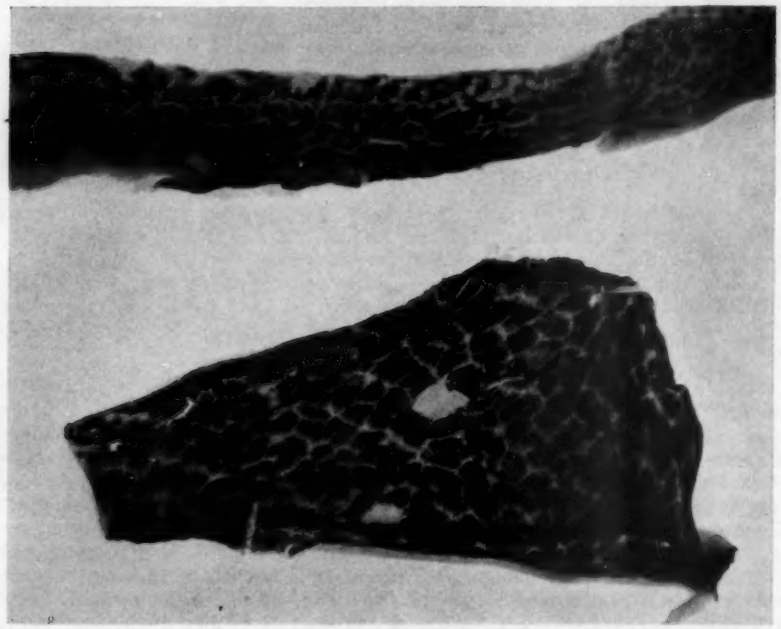
Examination of the blood revealed 3,130,000 erythrocytes and 114,000 leukocytes. A differential count of the latter disclosed an unusually large number of monocytes, from 20 to 50 per cent, according to different hematologists. Many myelocytes were also present.

A diagnosis of monocytic leukemia was made. This is considered to be a form of myelogenous leukemia. A number of cases of this form of leukemia have been reported in recent years.

The patient failed rapidly and died at home about four weeks after he was first seen. Permission to perform an autopsy was not obtained.

MELANOSIS OF THE COLON. ELLIS KELLERT.

A man 36 years old was operated on for a right inguinal hernia. In the course of the operation the appendix was removed. On section it showed marked melanosis. The patient reacted to the ether used as an anesthetic very poorly. On



Photograph of opened appendix and mucosa of colon showing pigmentation; slightly enlarged.

the second day after the operation, he became cyanotic; the pulse rate rose to 140 and was quite feeble. The blood pressure dropped to 70 systolic and 50 diastolic. Signs of pulmonary edema appeared, and he died on the fifth day after operation, apparently of respiratory failure.

The necropsy disclosed extensive pneumonitis as the cause of death. The colon was filled with dark brown fecal fluid and appeared normal except for the mucosa, which was brownish black and slightly thickened. The pigmentary change involved the mucosa of the entire large intestine but was most pronounced in the ascending colon. It ended abruptly at the iliocecal valve. The appendix was also involved. On close inspection, the deposit of pigment was found to present a fairly regular pattern, in which the brown areas resembled a mosaic, were from 2 to 3 mm. in diameter, and contained many minute punctate colorless areas, which corresponded apparently to the mouths of the intestinal glands.

Microscopically, the changes in the appendix and colon were identical. In the interglandular connective tissue, numerous lymphoid and plasma cells, such as one sees normally, were found. In addition, there were many cells filled with dark brown granules. These cells were irregularly distributed, varied considerably in size but were usually as large as active fibroblasts. They were pleomorphic and had poorly defined membranes. The nuclei were small, round or oval, and often situated eccentrically. The pigment granules also varied in size and frequently were so abundant as to obscure the nucleus. Pigmented cells were not present in the lymphoid tissue or in adjoining lymph nodes.

Book Reviews

Précis de Parasitologie. By E. Brumpt, membre de l'Académie de médecine, professeur a la Faculté de Médecine de Paris, Secretaire généeral de l'Institut de Médecine coloniale, directeur de l'École de malariologie de l'Université de Paris. Fifth edition. Two volumes. Price, 200 francs. Pp. 2,140, with 1,085 figures and 4 color plates. Paris: Masson & Cie, 1936.

In the present edition, Professor Brumpt has expanded his well known *Précis* to over 2,000 pages. The first part of the work, consisting of 102 pages, deals with parasitism and various generalities and includes discussions of types of parasitism, various phases of the physiologic processes of parasites, their life cycles, their production of disease, the defense reactions of the host, methods of diagnosis, treatment and prophylaxis. The remainder of the book is given to a detailed consideration of the protozoa, the spirochetes, the helminths, such arthropods as are parasites or vectors of parasites, and the fungi. He has attempted to make the book as complete a description as possible of the parasites and arthropods of medical importance. Comparatively little reference is made to related forms from animals. Even with the obvious necessity of limiting the field, some of the experimental work on animal parasites might have been included. This is particularly true with respect to the large mass of work on trypanosomes and malarial organisms.

The arrangement of the material on each parasite is excellent. There is generally a detailed description of the parasite and of its life cycle, an account of its habitat in the body and of the general lesions which it produces, and then an explanation of various experimental procedures, such as cultivation when possible and other methods of study. If the parasite is pathogenic, the symptoms which it produces, the complications, diagnosis, prognosis and treatment are discussed. In the chapters on the more important species, the methods of personal prophylaxis and of control of the disease are outlined.

Of particular interest is the section on the genus Entamoeba, in which Professor Brumpt gives a full account of his concept of the genus. He believes that the genus consists of three species, producing four-nucleate cysts: Endamoeba histolytica, the ability of which to produce severe lesions in man and cats is well known; Endamoeba dispar, which was first described by Brumpt and which is morphologically similar to E. histolytica but which only rarely ingests erythrocytes, is nonpathogenic for man and does not produce severe lesions in cats, and Endamoeba Hartmanni, which is nonpathogenic and does not infect cats. Many protozoologists consider all of these as belonging to E. histolytica. Should this concept prove correct, it would help to explain many puzzling facts in the wide distribution and seemingly frequent nonpathogenicity of the ameba causing dysentery, but it would make diagnosis extremely difficult, since E. dispar can be separated from E. histolytica only by experimental procedures and animal inoculations. (E. Hartmanni, however, can be differentiated by the small size of its cysts.)

Throughout, the specialist may question many of the author's ideas on classification and on valid species and sometimes the omission of recent work. The points of disagreement are, however, a resection of the tremendous difficulty any single author assumes when he tries to cover such a large field.

Professor Brumpt is to be congratulated on the general excellence of his treatment of the subject. The book is unique in giving, on one hand, accurate descriptions of the parasites and, on the other hand, accurate synopses of the pathologic evidence of parasitic disease, of the symptoms and of the methods of treatment in a way to be of real aid to the clinician. The work is profusely illustrated with diagrammatic, but in the main adequate, illustrations. The large number of original figures again exemplify the author's extensive experience in the field.

Autopsy Diagnosis and Technique. A Manual for Medical Students, Practitioners, Pathologists and Coroners' Physicians. By Otto Saphir, M.D., chairman, Nelson Morris Institute for Medical Research; pathologist, Michael Reese Hospital; associate professor of pathology, University of Illinois Medical School, Chicago. Foreword by Ludvig Hektoen, M.D. Pages 342, with 65 illustrations. New York: Paul B. Hoeber, Inc., 1937.

The first chapter deals with the autopsy permit, especially with the methods of obtaining it. The second chapter, on general technical considerations, includes a list and illustrations of the essential instruments. In the third chapter the list of diseases that may lead to sudden death without premonitory clinical symptoms is of particular interest.

The method of presentation is distinctive. The technic of every phase of the postmortem examination is described clearly and with all necessary details. After each step the author stops and describes the possible findings as an experienced pathologist would consider them in the process of an actual necropsy.

The medical student, the intern, the young assistant in a pathologic laboratory, the physician who has to perform a necropsy at rare intervals and the coroner's physician will profit from a study of this manual. The technic presented, which has been modified from Rokitansky's, has obvious advantages in that it will reduce the errors of omission if it is carried out step by step as presented.

A chapter on the external examination of the body and on the removal of organs is followed by chapters on the examination of the retroperitoneal structures, including the adrenal glands and the genito-urinary organs. Two instructive tables are found here, one dealing with the gross anatomic findings in different forms of diseases of the kidney, the other with clinical and laboratory findings. The examinations of the organs of the neck, the oral cavity, the esophagus, the larynx, trachea and bronchi, the organs of the chest, the gastro-intestinal tract and other organs of the abdominal cavity are then taken up, followed by the examination of the central nervous system, of the peripheral nerves and of the skeletal and muscle systems. A brief chapter on blood dyscrasias and a list of weights and measurements of organs conclude the book.

The drawings are clear and easily understood. Every one of the sixteen tables is a valuable summary of an important subject. The material is up to date and, thanks to the commendable brevity and lack of repetition, remarkably complete. The volume is handy, well put up in a flexible cover and well printed.

Juvenile Paresis. By William C. Menninger, M.D. The Menninger Clinic Monograph Series, no. 1. Price, $3. Cloth. Pp. 199, with 16 illustrations. Baltimore: Williams & Wilkins Company, 1936.

The comparative rarity of the juvenile form of dementia paralytica, which arises in apparently normal children, its protracted course, the peculiar histologic changes and the hopelessness of treatment, which, even with the use of malaria, may cause only a temporary slight improvement, are features in which this disease differs from the acquired or adult form. Being much less common, it is not so well known and understood, and therefore often remains undiagnosed. For these reasons, a review of the subject was needed. It has been well done in this book, the author of which is an indefatigable worker in this particular field, who has contributed a number of valuable studies in various periodicals. An extensive summary of these contributions and of the records in 43 cases from his own experience and 610 cases, reports of which he has found in the literature, forms the basis of the monograph. Each problem directly or indirectly pertaining to the subject is taken up in detail in separate chapters, and all are then well summarized. The method of description is largely statistical, but the reading is facilitated by reports of individual cases. The morphologic changes are presented adequately and are well illustrated. The bibliography of more than 500 references is practically complete. The monograph is a valuable contribution to the knowledge of a certain phase of neurosyphilis and will prove of service not only to special workers in this field but to physicians in general.

Books Received

SURGICAL PATHOLOGY OF THE THYROID GLAND. HERTZLER'S MONOGRAPHS ON SURGICAL PATHOLOGY. Arthur E. Hertzler, M.D., Surgeon to the Agnes Hertzler Memorial Hospital, Halstead, Kan., and Professor of Surgery, University of Kansas. Price, $5. Cloth. Pp. 298, with 238 illustrations. Philadelphia: J. B. Lippincott Company, 1936.

THE LUNG. William Snow Miller, Emeritus Professor of Anatomy, University of Wisconsin. Price, $7.50. Cloth. Pp. 212, with 152 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1936.

ANNUAL REPORT OF THE SURGEON GENERAL OF THE PUBLIC HEALTH SERVICE OF THE UNITED STATES FOR THE FISCAL YEAR 1936. Price, $1. Cloth. Pp. 158, with 4 illustrations. Washington, D. C.: Superintendent of Documents, 1936.

THE USE OF THE DEVELOPING EGG IN VIRUS RESEARCH. F. M. Burnet. Medical Research Council, Special Report Series, no. 220. Price, 1 shilling. Paper. Pp. 58, with 6 illustrations. London: His Majesty's Stationery Office, 1936.

A DIETARY SURVEY IN TERMS OF THE ACTUAL FOODSTUFFS CONSUMED. E. P. Cathcart and A. M. T. Murray. Medical Research Council Special Report Series, no. 218. Price, 1 shilling. Paper. Pp. 56. London: His Majesty's Stationery Office, 1936.

REPORTS OF THE COMMITTEE UPON THE PHYSIOLOGY OF HEARING. IV: THE USE OF HEARING AIDS. A. W. G. Ewing, I. R. Ewing and T. S. Littler. Medical Research Council, Special Report Series, no. 219. Paper. Price, 9 pence. Pp. 40. London: His Majesty's Stationery Office, 1936.

INFECTION BACILLAIRE ET LA TUBERCULOSE CHEZ L'HOMME ET CHEZ LES ANIMAUX. ÉTUDE BIOLOGIQUE ET EXPÉRIMENTALE VACCINATION PREVENTIVE. A. Calmette. Fourth edition, reviewed and completed by A. Boguet and L. Negre, chefs de service a l'Institut Pasteur de Paris. Price, 175 francs. Cloth. Pp. 1025, with 94 illustrations. Paris: Masson & Cie, 1936.

PERMÉABILITÉ EN PHYSIOLOGIE ET EN PATHOLOGIE GÉNÉRALE. E. Gellhorn, professeur de physiologie au Collége de médécine de Chicago, Université de l'Illinois (U. S. A.), and Jean Regnier, professeur agrégé a la Faculté de pharmacie de Paris, pharmacien-chef des hôpitaux de Paris. Price, 160 francs. Paper. Pp. 928. Paris: Masson & Cie, 1936.

CLINICAL ROENTGENOLOGY OF THE CARDIOVASCULAR SYSTEM: ANATOMY, PHYSIOLOGY, PATHOLOGY, EXPERIMENTS AND CLINICAL APPLICATIONS. Hugo Roesler, M.D., Associate Professor of Roentgenology and Cardiologist, Department of Medicine, Temple University School of Medicine; Cardiologist, Temple University Hospital; Consulting Cardiologist, Shriner's Hospital for Crippled Children, Philadelphia, Pennsylvania. Price, $7.50. Cloth. Pp. 343, with 199 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1937.

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ARCHIVES OF OPHTHALMOLOGY—Monthly. Includes original articles on diseases of the eye, abstracts from foreign and domestic literature, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): domestic, $8.00; Canadian, $8.40; foreign, $9.00. Single copies, 85 cents.

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